Short-Term Effects of Topical Tafluprost on Retinal Blood Flow in Cats

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Abstract

Purpose: The aim of this study was to determine the short-term effects of topical tafluprost, a novel prostaglandin $F_{2\alpha}$ derivative, on feline retinal circulation.

Methods: Seventeen (17) adult cats were anesthetized with enflurane and mechanically ventilated. One (1) drop of tafluprost (0.0015%; $n = 8$), latanoprost (0.005%; $n = 5$), or control vehicle ($n = 4$) was instilled in 1 eye and the fellow eye was untreated. We measured the intraocular pressure (IOP), vessel diameter, and blood velocity simultaneously for 120 min in the large retinal arterioles and calculated the retinal blood flow (RBF) with a laser Doppler velocimetry system.

Results: Tafluprost 0.0015% significantly increased RBF (maximum change, $42.8 \pm 4.2\%$ [mean $\pm$ standard error of the mean; $P < 0.01$) and blood velocity (maximum change, $24.1 \pm 3.3\%$; $P < 0.01$) for 120 min after instillation; there was no significant change in vessel diameter. Latanoprost 0.005% significantly increased RBF (maximum change, $31.7 \pm 3.4\%$; $P < 0.05$); there was no significant change in vessel diameter and blood velocity. There were no significant differences in the IOP reduction among the three groups.

Conclusions: We observed, for the first time, that topical tafluprost significantly increased RBF in cats, suggesting that dual-action tafluprost may be a beneficial antiglaucomatous agent for reducing IOP and increasing RBF.

Introduction

GLAUCOMA, WHICH IS THOUGHT TO BE a common optic neuropathy, often progresses despite well-controlled intraocular pressure (IOP). It is widely assumed that optic-nerve damage results from not only mechanical compression caused by elevated IOP, but also from impaired ocular blood flow.^{1,2} Thus, the improvement in ocular blood flow is considered meaningful for glaucoma therapy. The β -blockers, betaxolol and nipradilol, and the carbonic anhydrase inhibitor, dorzolamide, have been reported to improve optic nerve head (ONH) circulation in humans.^{3–5} The prostaglandin (PG) derivative, isopropyl unoprostone, was reported to increase^{6–8} or not affect⁹ ocular blood flow in humans. In addition, recent studies have reported that latanoprost, a $PGF_{2\alpha}$ analog, also was reported to increase^{7,10–20} or not affect^{21–27} ocular blood flow, including retinal blood flow (RBF),¹⁸ in various ocular regions and in various species.

Since tafluprost, a new $PGF_{2\alpha}$ derivative under development, is a highly selective and more potent prostanoid FP-

receptor agonist, compared with latanoprost, it is expected to be highly effective in reducing IOP by enhancing the uveoscleral outflow.^{28–31} Because the effect of tafluprost on ocular circulation has never been evaluated, we investigated its effect on RBF in cats.

Methods

Animal preparation

Protocols describing the use of cats were approved by the Animal Care Committee of Asahikawa Medical College (Asahikawa, Japan) and were in accordance with the Association for Research in Vision and Ophthalmology Statement for the Use of Animals in Ophthalmic and Vision Research. Seventeen (17) adult cats of either sex (weight, 2.6–5.6 kg) were used in the study. With the animals in a closed box, anesthesia was induced with enflurane, oxygen, and nitrous oxide, followed by an intraperitoneal injection of atropine (0.04 mg/kg). A tracheostomy was performed, and the ani-

mals were mechanically ventilated with 1.5–2.0% enflurane and room air. Catheters were placed in the femoral arteries and veins. Pancuronium bromide (0.1 mg/kg/h; Sankyo Pharmaceutical Co., Tokyo, Japan) was infused continuously. The animals were placed in the prone position, and the heads were fixed in a stereotaxic instrument. The arterial pH, partial pressure of arterial carbon dioxide, partial pressure of arterial oxygen, and hematocrit were measured intermittently with a blood-gas analyzer (Chiba Corning Co., Tokyo, Japan). The arterial blood pressure and heart rate were monitored continuously. The rectal temperature was maintained between 37 and 38°C with a heated blanket.

The pupils were dilated with 0.5% tropicamide and 0.5% phenylephrine sulfate (Santen Pharmaceutical Co., Ltd., Osaka, Japan). We already had confirmed that phenylephrine does not alter the retinal circulation in cats.^{32,33} A 0-diopter contact lens was placed on the cornea, which was protected with a drop of sodium hyaluronate (Healon; Pfizer Japan, Inc., Tokyo, Japan). A 26-gauge butterfly needle was inserted into the anterior chamber and connected to a pressure transducer to monitor the IOP.

RBF measurement

We measured the RBF by using a laser Doppler velocimetry system (Laser Blood Flowmeter model 100; Canon, Inc., Tokyo, Japan) that was customized for use in cats. The instrument, which is similar to a fundus camera, is designed to measure vessel diameter and blood velocity simultaneously in retinal vessels and to calculate the RBF. Diode (wavelength, 670 nm) and helium-neon lasers (wavelength, 543 nm) were used to measure the blood velocity and the vessel diameter, respectively. The diode laser was focused on the center of a vessel, and the helium-neon laser was positioned vertically to a vessel by direct visualization.

The principles of the laser Doppler velocimetry system have been described in detail elsewhere.^{32–36} Briefly, the blood velocity was measured by bidirectional laser Doppler velocimetry, which provides absolute measurements of the speed of the red blood cells (RBCs) flowing at discrete, selected sites in the retinal vessels, assuming Poiseuille's flow.^{37,38} The diode laser illuminates a retinal vessel at the same position. The Doppler-shifted light scattered from the RBCs flowing in the retinal ves-

sels is detected simultaneously in two directions and separated by a fixed angle. The signals from the two photomultiplier tube detectors undergo computer-controlled spectrum analysis and sequential measurement of the maximum speed ($V_{\max}$) at the center of the vessels. In the laser Doppler velocimetry system, each pair of spectra was recorded, and the $V_{\max}$ was calculated automatically every 5 msec for 1 sec during each measurement. The $V_{\max}$ was defined as the averaged $V_{\max}$ during one cardiac cycle. Measurement sites were generally between the first and second bifurcations.

The diameter of the retinal vessel was determined automatically by computer analysis of the signal produced by the image of the vessel. The vessel images were captured every 4 msec for 60 msec just before and after the blood-velocity measurement. Using microdensitometry, the captured images were analyzed to obtain the vessel diameter by using the half height of the transmittance profile to define the vessel edge.³⁹ The value of the vessel diameter was defined as the average of the values determined at each time point.

The mean arterial blood pressure (MABP) was calculated as 1/3 systolic arterial blood pressure + 2/3 diastolic arterial blood pressure. The RBF was calculated from the formula:

$$\text{RBF} = S \times V_{\text{mean}}$$

where S is the cross-sectional area of the retinal artery at the laser Doppler measurement site, assuming a circular cross-section, and V_{mean} is the mean blood velocity calculated as $V_{\text{mean}} = V_{\max}/2$.⁴⁰ The ocular perfusion pressure (OPP) was calculated as 2/3 MABP – IOP.⁴¹

Application of ophthalmic solution and protocol

Tafluprost (0.0015%) and latanoprost (0.005%) ophthalmic solution were provided by Santen Pharmaceutical Co., Ltd., and Pfizer Japan Inc., respectively. With a micropipette, 30 μL of tafluprost (0.0015%; $n = 8$), latanoprost (0.005%; $n = 5$), or control vehicle ($n = 4$) was instilled into the right eyes in a masked manner. The contralateral eyes were untreated.

The RBF measurements started 15 min before the application of each drug; an average of five measurements at 1-min intervals was defined as the baseline value before the instillation. After the instillation, measurements were per-

TABLE 1. CHANGES IN SYSTEMIC AND OCULAR PARAMETERS

Parameter	Vehicle (n = 4)		Tafluprost 0.0015% (n = 8)		Latanoprost 0.005% (n = 5)	
	Before	120 min	Before	120 min	Before	120 min
pH	7.36 $\pm$ 0.19	7.37 $\pm$ 0.20	7.37 $\pm$ 0.21	7.35 $\pm$ 0.18	7.39 $\pm$ 0.16	7.38 $\pm$ 0.23
PaCO ₂ (mmHg)	31.1 $\pm$ 1.1	31.6 $\pm$ 0.9	32.2 $\pm$ 1.4	31.6 $\pm$ 1.3	31.8 $\pm$ 1.3	30.8 $\pm$ 1.2
PaO ₂ (mmHg)	109.6 $\pm$ 3.6	112.0 $\pm$ 4.4	110.3 $\pm$ 3.0	113.6 $\pm$ 2.7	102.0 $\pm$ 3.4	104.3 $\pm$ 4.1
Hematocrit (%)	31.0 $\pm$ 1.1	30.3 $\pm$ 1.4	31.9 $\pm$ 1.6	32.0 $\pm$ 2.0	29.9 $\pm$ 1.7	30.2 $\pm$ 2.2
MABP (mmHg)	95.8 $\pm$ 3.2	91.1 $\pm$ 3.6	86.6 $\pm$ 3.5	83.2 $\pm$ 3.0	93.3 $\pm$ 3.0	92.5 $\pm$ 2.7
IOP (mmHg)	13.3 $\pm$ 1.3	9.0 $\pm$ 1.5*	15.6 $\pm$ 1.9	12.1 $\pm$ 1.6*	17.7 $\pm$ 1.1	13.9 $\pm$ 1.0*
OPP (mmHg)	50.5 $\pm$ 2.5	51.7 $\pm$ 3.1	42.1 $\pm$ 2.7	43.4 $\pm$ 2.5	44.5 $\pm$ 2.5	47.8 $\pm$ 2.3*
HR (beats/min)	150.7 $\pm$ 7.8	145.7 $\pm$ 8.0	141.4 $\pm$ 9.4	145.5 $\pm$ 9.9	139.5 $\pm$ 8.1	144.2 $\pm$ 6.9

PaCO₂, partial pressure of arterial carbon dioxide; PaO₂, partial pressure of arterial oxygen; MABP, mean arterial blood pressure; HR, heart rate; Before, before instillation; 120 min, 120 minutes after instillation.

Note. Data are expressed as the means $\pm$ standard error.

* $P < 0.05$ versus values before instillation by a paired Student t -test.

formed every 10 min for 120 min. At each time point, three successive measurements were taken, and the average of the three measurements was recorded.

Statistical analysis

All data are expressed as the mean $\pm$ standard error of the mean. For statistical analysis, we used one-way analysis of variance (ANOVA), followed by post-hoc comparison with the Dunnett procedure. Differences between the means in systemic parameters before and 120 min after instillation were assessed with the Student paired *t*-test. In all cases, $P < 0.05$ was considered significant.

Results

There were no significant differences in the arterial pH, the partial pressure of arterial oxygen, the partial pressure of arterial carbon dioxide, the hematocrit, and the mean heart rate between the before and after instillations of tafluprost, its vehicle, and latanoprost (Table 1). There was no significant change in MABP during the measurements.

One hundred twenty (120) min after the instillation of tafluprost 0.0015%, the vessel diameter, blood velocity, and RBF increased by $3.5 \pm 2.1\%$ (from 90.1 ± 2.3 to $93.2 \pm 2.3 \mu\text{m}$; $P > 0.05$, compared with the value in the vehicle group at the same time point), $12.2 \pm 3.0\%$ (from 16.0 ± 1.5 to $17.9 \pm 1.5 \text{ mm/sec}$; $P = 0.042$), and $18.1 \pm 3.6\%$ (from 3.0 ± 0.8 to $3.5 \pm 0.7 \mu\text{L/min}$; $P = 0.017$), respectively (Fig. 1). The vessel diameter tended to increase only slightly during the measurement. The blood velocity increased to a maximum level 40 min after the instillation of tafluprost 0.0015%, and that level was maintained until 120 min after instillation. The RBF reached a maximum level 50 min after instillation and then decreased slightly, but the increased level was maintained up to 20% until 120 min after instillation.

The instillation of latanoprost 0.005% resulted in increased vessel diameter, blood velocity, and RBF by $8.1 \pm 3.2\%$ (from 101.9 ± 3.6 to $110.5 \pm 4.4 \mu\text{m}$; $P > 0.05$, compared with the value in the vehicle group at the same time point), $3.4 \pm 3.1\%$ (from 20.2 ± 2.4 to $20.7 \pm 2.3 \text{ mm/sec}$; $P > 0.05$), and $18.5 \pm 3.5\%$ (from 5.1 ± 1.5 to $5.9 \pm 1.5 \mu\text{L/min}$; $P = 0.049$), respectively. The vessel diameter and blood velocity tended to increase slightly, but not significantly, during latanoprost treatment. The elevated RBF showed the maximum response 90 min after the instillation of latanoprost.

The incremental changes in velocity and RBF in the tafluprost 0.0015% group tended to be higher than those of the latanoprost 0.005% group at most measurement points but did not reach significance. In addition, tafluprost seems to cause an increase in the RBF faster than latanoprost (Fig. 1). Indeed, the group-averaged values of the mean times in which the maximum RBF changes were observed in the tafluprost 0.0015% and latanoprost 0.005% groups were 62.5 ± 5.6 and 82.0 ± 3.9 min, respectively.

Figure 2 shows the tafluprost 0.0015%, its vehicle, and the latanoprost 0.005% group averages of the maximum changes in retinal circulatory parameters (e.g., diameter, velocity, and RBF). Because there were some differences in the time course of the response to the drug in each cat, we defined as the maximum change that observed after instillation from the baseline value to prevent underestimation of the degree of

FIG. 1. Time course of the changes in retinal circulation after topical instillation of tafluprost 0.0015%, its vehicle, and latanoprost 0.005%. Data are presented as the mean $\pm$ the standard error of the mean. Significant differences, compared with the vehicle at each time point, are indicated (* $P < 0.05$) by one-way analysis of variance, followed by Dunnett's procedure.

the response. The maximum changes in the blood velocity in the tafluprost 0.0015% and latanoprost 0.005% groups were 24.1 ± 3.3 ($P = 0.007$, compared with the value in the vehicle group) and $16.6 \pm 3.2\%$ ($P > 0.05$), and the maximum changes in the RBF were 42.8 ± 4.2 ($P = 0.002$) and $31.7 \pm 3.4\%$ ($P = 0.040$), respectively.

There was no significant difference in IOP values before instillation among the three groups. The IOP values decreased and the ocular perfusion pressure (OPP) values increased gradually during the 120 min after instillation in all groups, compared with the pretreatment values (Table 1). There were no significant differences in the IOP-lowering effect between tafluprost 0.0015% or latanoprost 0.005% and the control group throughout the evaluation. There was a significant increase in OPP only in the latanoprost 0.005% group.

FIG. 2. Effects of tafluprost 0.0015%, its vehicle, and latanoprost 0.005% in retinal circulation. Data are presented as the mean $\pm$ the standard error of the mean. Significant differences, compared with the vehicle at each time point, are indicated (* $P < 0.05$, ** $P < 0.01$) by one-way analysis of variance, followed by Dunnett's procedure.

Discussion

We observed that one instillation of 1 drop of tafluprost 0.0015% increased RBF and blood velocity during 120 min after instillation, and that there were significant differences compared with the control group. With latanoprost 0.005%, the changes in the parameters of the retinal circulation tended to be slightly smaller than the changes observed with tafluprost 0.0015%. The increased RBF was caused mainly by the increased blood velocity at the measurement site, because the vessel diameter did not change substantially. Therefore, the observed increase in blood velocity might reflect a dilation of the downstream vessels. Taken together, we speculated that retinal microvessels located more peripherally than the points measured in this study might be dilated. Sponsel et al. reported that latanoprost increased the mid-peripheral retinal capillary microcirculation in humans, as measured by scanning laser Doppler flowmetry,¹⁸ which is consistent with our results.

Liu et al. reported that topical latanoprost increased the pulsatile ocular blood flow (POBF) in patients with normal-tension glaucoma. However, the increase in the POBF might be caused by an increase in OPP caused by the reduction of IOP, because the changes in POBF no longer reached statistical significance after adjusting for the IOP.¹⁴ The OPP increased significantly in the latanoprost group but did not change in the tafluprost group (Table 1). Because there is a mechanism that autoregulates the RBF, the change in OPP observed in the latanoprost group seemed to have little effect on the increase in RBF.

The current results suggested that tafluprost might be more effective than latanoprost in increasing the RBF (Fig. 2). Sjoquist et al. reported that 30 min after topical applica-

tion, the concentration of latanoprost was approximately 10^{-8} M in the retina and choroid in Cynomolgus monkeys.⁴² Stjernschantz et al. reported that high doses of latanoprost tended to cause incremental changes in RBF in monkeys, but there were no significant changes.²⁷ The affinity for the prostanoid FP-receptor of tafluprost acid was reported to be 12 times that of latanoprost and 1700 times that of isopropyl unoprostone.³⁰ Regarding the molecular structure, latanoprost has the hydroxyl group at position 15, which is reported to be dehydrogenated and inactivated by NADP⁺-dependent 15-hydroxyprostaglandin dehydrogenase.⁴³ On the other hand, tafluprost is a 15,15-difluoro PGF_{2 α} derivative, which is not affected by this enzyme and more stable *in vivo*, compared with latanoprost. Therefore, these results suggested that the increased RBF resulting from the instillation of tafluprost might be related to the high affinity of tafluprost to the FP-receptors and the drug's structural characteristics.

Certain PGs, such as PGI₂ and PGE₂, usually act as vasodilators in many species.⁴⁴ However, PGF_{2 α} may exert different actions on blood vessels, depending on the species and tissues.²⁷ Ishikawa et al. reported that latanoprost caused endothelium-independent vasodilation in isolated ciliary arteries in rabbits.⁴⁵ Ishii et al.^{12,13} reported that latanoprost increased the circulation of the optic nerve head tissue in monkeys, rabbits, and humans and speculated that PGF_{2 α} caused vasodilation through the PGI₂ released from the subendothelial tissue, since the intravenous injection of indomethacin prevented an increase in the circulation of the optic nerve head in animals. Indeed, PGF_{2 α} exerts vasodilatory effects through PGI₂ in canine uterine arteries.⁴⁶ Regarding differences among species, Stjernschantz et al. reported that PGF_{2 α} had more extensive microvascular effects in rabbits and cats, compared with primate eyes, such as in monkeys.²⁷ Although we did not examine the effect of PG-receptor blockers in the current study, the increased RBF caused by tafluprost might result from the release of PGs. Further study using PG-receptor antagonists is needed to reveal the mechanism of the vasodilatory effect of tafluprost.

The retinal construction and circulation in cats are similar to those in humans, compared with small animals, such as rats. However, the microvasculature effects of PGF_{2 α} in cats are reported to be stronger than those in primate animals.²⁷ Moreover, the degree of vascular reaction between cats and humans does not seem to be similar after the instillation of the same amount of solution, because the ocular volumes differ. Therefore, the change in RBF in humans may differ, or be attenuated, compared with those in cats.

Many studies have reported that PG analogs, especially isopropyl unoprostone and latanoprost, increase the ocular blood flow in various species.^{6-8,10-20} In the current study, we compared the vasodilatory effects of latanoprost with those of tafluprost. Although the mechanism is not fully understood, it has been reported that latanoprost increased^{7,10-20} or did not affect²¹⁻²⁷ the ocular blood flow. The current results that latanoprost increased RBF (Fig. 2) seem consistent with those results.

In the current study, the IOP decreased gradually during 120 min after instillation in all groups, although there were no significant differences in the decrease in IOP among the groups. It is well known that enflurane has substantial IOP-lowering properties.^{47,48} Nakajima et al. reported that topical

tafluprost did not change the IOP up to 2 h after instillation but reduced the IOP significantly 4 h after instillation in monkeys.²⁸ These results suggest that the apparent effect of topical tafluprost on IOP reduction might take longer, compared with the effect on the retinal circulation. In addition, the effect of PGF_{2α} on IOP reduction was reported to be weak in healthy cats.⁴⁹ Taken together, we speculated that the IOP reduction had little effect on the retinal circulatory response to topical tafluprost in healthy cats.

Conclusions

In conclusion, our findings showed, for the first time, that topical tafluprost increased the RBF in cats. Although these results cannot be extrapolated directly to humans and the mechanism needs to be clarified, this result is noteworthy and may be beneficial regarding the effect of antiglaucomatous agents on the ocular circulation.

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