Effects of Travoprost Eye Drops on Intraocular Pressure and Pulsatile Ocular Blood Flow: A 180-Day, Randomized, Double-Masked Comparison with Latanoprost Eye Drops in Patients with Open-Angle Glaucoma

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ABSTRACT

Background: Because of the increasing realization of the importance of optic nerve head perfusion in the pathogenesis of glaucoma, the influence of new antiglaucomatous drugs on ocular hemodynamic properties should be investigated.

Objective: The aim of this study was to compare the effects of 2 prostaglandin analogues, travoprost eye drops and latanoprost eye drops, on intraocular pressure (IOP) and pulsatile ocular blood flow (pOBF) in patients with primary open-angle glaucoma (POAG).

Methods: Previously untreated patients aged 40 to 60 years with POAG and normal brachial blood pressure (BBP), heart rate, body mass index, and hemorheologic findings were eligible for this randomized, double-masked study. Two drops of travoprost (group T) or latanoprost (group L) were self-administered in both eyes at 9:00 PM. In all patients, IOP, pOBF, BBP, and heart rate were measured at baseline and on days 15, 30, 60, 90, and 180 of treatment.

Results: Twenty-five consecutive patients with POAG were enrolled in this study conducted at the Glaucoma Research Center of the Department of Ophthalmology, Bari University, Policlinico di Bari (Bari, Italy). Of these, 7 were withdrawn because they did not return for the second appointment, leaving 18 patients (11 men, 7 women; mean [SD] age, 51.9 [5.5] years) to complete the study. In both groups, mean IOP values were significantly reduced at all time points compared with baseline (all $P < 0.01$). Mean pOBF values increased ~50% from baseline following treatment with either travoprost or latanoprost by day 15, were maintained at that level for 60 days, and then gradually decreased (group T: $P = \text{NS}$, NS , <0.01 , <0.05 , and <0.05 at days 15, 30, 60, 90, and 180, respectively, vs baseline; group L: $P < 0.01$ at all time points vs baseline).

All other parameters remained constant throughout the study. An early inverse correlation between IOP and pOBF was noted in group T but not in group L. No significant differences were found between groups in IOP or pOBF at any time point.

Conclusions: In this study population, pOBF was increased with travoprost and latanoprost in the short term, but this effect was kept constant only with travoprost. IOP was reduced with both drugs after short-term therapy, and this reduction was maintained in both groups. Travoprost may represent another option for the medical treatment of POAG. (*Curr Ther Res Clin Exp.* 2003;64:389–400) Copyright © 2003 Excerpta Medica, Inc.

Key words: travoprost, latanoprost, pulsatile ocular blood flow, intraocular pressure, primary open-angle glaucoma.

INTRODUCTION

Because of the increasing realization of the importance of optic nerve head perfusion in the pathogenesis of glaucoma, the influence of new antiglaucomatous drugs on ocular hemodynamic properties should be investigated.¹ We searched for articles on primary open-angle glaucoma (POAG) using MEDLINE (key words searched: *nerve head perfusion, glaucoma, ocular blood flow, hemodynamic, antiglaucomatous drugs, travoprost, and latanoprost*; years searched: 1998–2002), as well as all materials available in the Bari University library (key words searched: same as above; years searched: 1985–2002). Our search revealed that in recent studies, latanoprost eye drops were reported to increase ocular blood flow (by acting on the prostaglandin F [PGF] vascular receptor^{2–5}) and to reduce intraocular pressure (IOP).^{6–8} Compared with PGF20 isopropyl ester, travoprost eye drops showed a more selective affinity for the PGF receptor with fewer severe adverse events (AEs),⁹ offering superior IOP reduction and diurnal control.^{10,11} However, to date no studies have examined the effects of this drug on ocular hemodynamic properties.

Considering the importance of ocular blood flow in the pathogenesis of glaucoma, we compared the effects of travoprost and latanoprost eye drops on IOP and pulsatile ocular blood flow (pOBF) in patients with POAG.

PATIENTS AND METHODS

Patients regularly attending the Glaucoma Research Center of the Department of Ophthalmology at Bari University, Policlinico di Bari (Bari, Italy), between January and March 2002 were eligible for this randomized, double-blind study. The independent ethics committee of the Policlinico approved the study, and written informed consent was obtained from all patients.

At their first appointment at the center, consecutive patients with POAG were enrolled in the study. The POAG diagnostic criteria were glaucomatous

visual field loss, pathologic optic disc cupping or notching, an open drainage angle, IOP >20 mm Hg without topical treatment, and a tonometric curve that ruled out normotensive glaucoma.

To avoid the influence of ocular and general factors that could affect pOBF measurements, we adopted the following ocular inclusion criteria: refraction of ± 3 diopters (D); absence of previous ocular hypotensive treatments; and progression of visual field loss documented by at least 3 full-threshold 30-2 visual field tests with the Humphrey Field Analyzer model 606 (Zeiss Humphrey Systems, San Leandro, California) in the previous year. The score on the full-threshold visual field test was based on the Humphrey visual field rating criteria.¹² Patients with other kinds of glaucoma were excluded from the study.

Patients were eligible for the study if they met the following criteria: non-smoker; age 40 to 60 years; systolic brachial blood pressure (BBP) 120 to 140 mm Hg; diastolic BBP 70 to 90 mm Hg; heart rate 66 to 80 beats/min; body mass index appropriate for sex and age; and normal hemorheologic parameters (hematocrit, hemoglobin concentration, plasma iron concentration, leukocyte count, platelet count). Patients could not have any cardiovascular abnormalities (eg, atherosclerosis or carotid stenosis) or be taking systemic vasoactive therapy (eg, aspirin, calcium antagonists, nitroglycerin derivatives, oral beta-blockers).

Patients who met all of the inclusion criteria were block-randomized, to improve the distribution of patients during follow-up, to the travoprost* group (group T) or the latanoprost† group (group L). The labels were removed from the bottles, identical in appearance, containing the eye drops so that patients would not know which drug they were receiving. Patients were instructed to self-administer 2 drops in both eyes once daily at 9:00 PM.

IOP and pOBF were determined with patients seated after a 5-minute rest period, using the Langham pOBF tonograph (Langham Ophthalmic Technologies, Timonium, Maryland). Measurements were taken at 10:00 AM at baseline and on days 15, 30, 60, 90, and 180 of treatment. Blood pressure and heart rate also were measured at all of these time points. To minimize bias, all of the examinations were carried out by one of the authors (M.V.), who had considerable experience using the instruments. The physician who performed the IOP and pOBF measurements was masked to patient treatment. According to the protocol suggested by Langham et al¹³ to measure pOBF, the probe was mounted on a slit-lamp and was gently pushed onto the previously anesthetized corneal apex. The instrument automatically took 5 measurements, and the mean value was determined.

AEs were monitored at the same time points as the pOBF measurements. Investigators monitored objective signs and patients spontaneously reported

*Trademark: Travatan® (Alcon, Inc., Dallas, Texas).

†Trademark: Xalatan® (Pharmacia Corp., Uppsala, Sweden).

subjective symptoms. Patients were questioned about the occurrence of a set of primary AEs (conjunctival hyperemia, conjunctival papillae, stinging, burning, and foreign-body sensation).

Statistical Analysis

The mean IOP and pOBF values were calculated before and after treatment. Variation within each group was determined using the Bonferroni and Dunnett multiple comparison tests (control: baseline) and between groups using the unpaired *t* test. To assess the effect of the eye drops on ocular pressure, the Pearson product moment correlation was calculated for IOP and pOBF at each time point. Differences were considered significant at $P \leq 0.05$ (2-tailed test). All analyses were performed using GraphPad InStat® version 3.05 (GraphPad Software, Inc., San Diego, California).

RESULTS

Twenty-five consecutive patients with POAG were enrolled in the study. Of these, 7 were withdrawn because they did not return for the second appointment. The baseline characteristics of the 18 remaining patients (11 men, 7 women; mean [SD] age, 51.9 [5.5] years) are shown in Table I.

The IOP and pOBF values are shown in Tables II and III, respectively. The mean (SD) IOP and pOBF values are shown in Figures 1 and 2, respectively, and Table IV.

In both groups, mean IOP was significantly decreased compared with baseline at all time points (all $P < 0.01$). No statistically significant between-group differences in IOP were found at baseline or at any time point throughout the study.

Table I. Baseline demographic and clinical characteristics by treatment group. (Data are given as mean [SD] unless otherwise indicated.)

Characteristic	Travoprost (n = 9)	Latanoprost (n = 9)
Age, y (range, 46–60)	52.3 (5.2)	51.6 (4.2)
Sex, no. (%)		
Men	5 (55.6)	6 (66.7)
Women	4 (44.4)	3 (33.3)
Systolic BBP, mm Hg	132.4 (7.9)	130.3 (8.5)
Diastolic BBP, mm Hg	85.0 (8.4)	86.1 (8.0)
Heart rate, beats/min	82.8 (5.8)	81.8 (5.9)
Eyes, n	18	18
Refraction, median (SE), diopters	0.70 (1.14)	0.67 (0.77)
IOP, mm Hg	23.7 (2.8)	24.1 (2.9)
pOBF, $\mu\text{L}/\text{min}$	709.8 (284.1)	680.8 (88.4)
Cup-to-disk ratio	0.44 (0.07)	0.43 (0.09)

BBP = brachial blood pressure; IOP = intraocular pressure; pOBF = pulsatile ocular blood flow.

Table II. Intraocular pressure (IOP) (mm Hg) and pulsatile ocular blood flow (pOBF) ($\mu\text{L}/\text{min}$) in the travoprost group at baseline and throughout the treatment period.

Patient No./Eye	Baseline		Day 15		Day 30		Day 60		Day 90		Day 180	
	IOP	pOBF	IOP	pOBF	IOP	pOBF	IOP	pOBF	IOP	pOBF	IOP	pOBF
1/Left	27	463	22	1021	21	758	17	1092	19	1159	16	840
1/Right	25	916	18	1068	20	1190	15	1420	18	1454	16	1160
2/Left	22	724	18	1013	19	840	14	888	16	1026	15	876
2/Right	22	792	20	1033	19	969	17	687	15	962	17	851
3/Left	25	537	25	485	20	570	22	728	18	793	20	693
3/Right	24	710	22	865	19	659	16	1077	18	683	20	695
4/Left	22	576	19	754	19	811	15	998	14	853	14	812
4/Right	25	644	20	721	17	892	17	785	16	898	16	852
5/Left	23	496	16	1105	17	753	16	843	18	922	18	770
5/Right	21	470	16	917	15	947	15	1296	18	835	17	765
6/Left	19	734	13	935	15	1065	16	954	16	754	15	702
6/Right	22	629	14	1057	16	914	17	1008	17	1041	16	994
7/Left	32	366	21	713	15	710	14	694	14	783	14	758
7/Right	25	374	21	570	15	721	17	711	17	652	17	720
8/Left	25	853	16	2576	16	2380	18	2406	12	1781	14	1251
8/Right	23	829	16	1026	15	1622	18	1496	14	1581	14	1114
9/Left	22	1157	16	1360	17	1171	14	1107	15	1310	15	1240
9/Right	22	1506	15	1291	18	1510	14	1677	15	1595	15	1535

Table III. Intraocular pressure (IOP) (mm Hg) and pulsatile ocular blood flow (pOBF) ($\mu\text{L}/\text{min}$) in the latanoprost group at baseline and throughout the treatment period.

Patient No./Eye	Baseline			Day 15			Day 30			Day 60			Day 90			Day 180		
	IOP	pOBF		IOP	pOBF		IOP	pOBF		IOP	pOBF		IOP	pOBF		IOP	pOBF	
10/Left	25	754		20	1021		17	980		17	970		17	990		25	754	
10/Right	22	816		20	1068		15	1104		16	1100		16	920		22	816	
11/Left	26	670		19	1013		18	840		16	820		16	990		26	670	
11/Right	24	745		18	1033		17	969		15	964		17	962		24	745	
12/Left	22	650		20	980		20	1045		18	995		20	820		22	650	
12/Right	28	760		19	1110		18	1000		18	1100		20	880		28	760	
13/Left	24	743		18	1012		15	990		14	998		16	950		24	743	
13/Right	26	756		17	1020		17	892		15	1045		16	898		26	756	
14/Left	23	540		17	940		16	990		18	843		18	922		23	540	
14/Right	21	570		15	917		15	947		18	800		17	835		21	570	
15/Left	18	780		15	1090		16	941		16	954		15	996		18	780	
15/Right	22	740		16	1057		17	914		17	920		17	1041		22	740	
16/Left	31	644		15	950		14	980		14	896		16	880		31	644	
16/Right	26	687		15	990		17	1010		17	1045		17	880		26	687	
17/Left	25	520		16	890		18	900		15	960		14	960		25	520	
17/Right	23	670		16	1026		18	890		14	960		14	920		23	670	
18/Left	23	560		17	980		16	870		15	1000		16	990		23	560	
18/Right	24	650		18	1021		16	992		15	890		15	840		24	650

Figure 1. Mean (SD) intraocular pressure (IOP) values by treatment group at baseline (day 0) and throughout the study. $P < 0.01$ at all time points versus baseline in both groups. No significant between-group differences were found.

Figure 2. Mean (SD) pulsatile ocular blood flow (pOBF) values by treatment group at baseline (day 0) and throughout the study. $*P < 0.01$ versus baseline. $†P < 0.05$ versus baseline. No significant between-group differences were found.

In group T, the mean pOBF increased 44.9% by day 15 and was maintained at that level throughout the remainder of the study ($P = \text{NS}$, NS , <0.01 , <0.05 , and <0.05 at days 15, 30, 60, 90, and 180, respectively, vs baseline). In group L, mean pOBF increased 47.9% by day 15, was maintained at that level for 60 days, and then progressively decreased throughout the remainder of the study ($P < 0.01$ at all time points vs baseline). A between-group comparison did not show any statistically significant differences in pOBF at any time point.

In group T, an inverse correlation was noted at day 15 ($r = -0.49$; $P = 0.04$), whereas in group L a correlation was noted only at 180 days of treatment ($r = -0.46$; $P = 0.05$) (Table V).

Two patients in group L (22.2%) and 3 in group T (33.3%) developed treatment-related conjunctival hyperemia and itching, both of which resolved spontaneously after 3 weeks of therapy.

DISCUSSION

The prostaglandin analogues latanoprost and travoprost have favorable ocular and systemic safety profiles and are well tolerated.^{10,14,15} IOP control should not be the sole aim of modern glaucoma therapy. A hypotensive agent that enhances blood flow to the eye and provides neuroprotection would be an optimal therapy because visual field loss continues in some patients despite successful medical or surgical reduction of IOP.¹⁶

Measurement of pOBF may provide an indirect estimate of optic nerve blood flow.^{17,18} pOBF is estimated from the ocular pulse, which is directly proportional to perfusion pressure and inversely related to vascular resistance. Although this pulse mostly reflects choroidal blood flow, the choroidal system is also the main contributor to optic nerve blood flow, accounting for 90% of choroidal circulation but for only 10% of retinal circulation.^{19,20} The extent of choroidal perfusion varies with the particular glaucoma treatment, and this has a direct effect on optic nerve head perfusion. Therefore, antiglaucomatous treatments can influence long-term tropism of the optic nerve head,^{21,22} which may be important because pOBF values have been shown to be reduced in patients with POAG.²³ Previous studies^{11,24,25} have demonstrated the efficacy of travoprost and latanoprost in reducing IOP, but none of them have compared the effect on choroidal perfusion. Referring to a previous protocol to assess the influence of brimonidine (ophthalmic) on pOBF,²⁶ we analyzed the effect of travoprost and latanoprost on choroidal perfusion. We demonstrated that treatment with travoprost or latanoprost has a beneficial effect on pOBF, increasing the average flow by day 15 after beginning treatment; moreover, both prostaglandin analogues significantly decreased IOP by day 15 of therapy. The increase in pOBF can be interpreted as a direct consequence of the IOP reduction.^{27,28}

Subsequent flow variations might be related to capillary autoregulation, which is known to exist in the retina and hypothesized to exist in the choroid.²⁹ The diameter of the capillary vessels may change according to perfusion

Table IV. Mean (SD) values for intraocular pressure (IOP) and pulsatile ocular blood flow (pOBF) by treatment group at baseline and throughout the study.*†

Time Point	Travoprost	Latanoprost
Baseline		
IOP	23.7 (2.8)	24.1 (2.9)
pOBF	709.8 (284.1)	680.8 (88.4)
Day 15		
IOP	18.2 (3.2)	18.6 (3.7)
pOBF	1028.3 (447.5)‡	1006.6 (57.7)
Day 30		
IOP	17.4 (2.0)	17.3 (1.8)
pOBF	1026.8 (438.9)‡	958.6 (66.0)
Day 60		
IOP	16.3 (2.0)	16.7 (1.5)
pOBF	1103.7 (434.7)	958.9 (86.6)
Day 90		
IOP	16.1 (1.9)	16.0 (1.5)
pOBF	1060.1 (343.4)§	926.3 (63.0)
Day 180		
IOP	16.1 (1.9)	16.5 (1.7)
pOBF	923.8 (240.4)§	833.8 (85.9)

*No statistically significant between-group differences were found (unpaired *t*-test).

†*p* < 0.01 versus baseline (Dunnnett multiple comparison test) unless otherwise indicated.

‡*p* = NS versus baseline.

§*p* < 0.05 versus baseline.

Table V. Linear correlation between intraocular pressure and pulsatile ocular blood flow in the 2 treatment groups at baseline and throughout the study.

Time Point	Travoprost		Latanoprost	
	<i>r</i> *	<i>P</i>	<i>r</i> *	<i>P</i>
Baseline	−0.39	0.11	−0.48	0.85
Day 15	−0.49	0.04	−0.05	0.82
Day 30	−0.28	0.26	0.38	0.12
Day 60	−0.05	0.85	0.19	0.45
Day 90	−0.42	0.08	−0.20	0.40
Day 180	−0.49	0.04	−0.46	0.05

*Pearson product moment correlation.

pressure. This could explain the pOBF reduction with time, although pOBF was still increased at 180 days of treatment with latanoprost and travoprost compared with baseline. Considering the influence of IOP on pOBF, only travoprost increased pOBF, reducing IOP. This inverse correlation could be explained by greater specificity of travoprost than latanoprost on IOP and pOBF regulation. In any case, capillary autoregulation may impair this mechanism after 30 days of therapy. After 180 days, other factors seem to reactivate the correlation between IOP and pOBF predominantly in patients treated with travoprost.²⁹ Unfortunately, our data are not adequate because of the short follow-up and the small number of patients to make conclusions regarding tolerability or effects on pOBF. Therefore, additional studies are needed.

All of the patients enrolled in this study had normal hemorheologic values. Because some patients may have vasculopathy and other systemic diseases, it may not be accurate to extrapolate our results to the general patient population.

CONCLUSIONS

In this study population, pOBF was increased with travoprost and latanoprost in the short term, but this effect was kept constant only with travoprost. IOP was reduced with both drugs after short-term therapy, and this reduction was maintained in both groups. Travoprost may represent another option for the medical treatment of POAG.

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