A Six-month, Randomized, Double-masked Study Comparing Latanoprost with Timolol in Open-angle Glaucoma and Ocular Hypertension

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Purpose: To compare the intraocular pressure (IOP)-reducing effect and side effects of 0.005% latanoprost administered once daily with 0.5% timolol administered twice daily in patients with open-angle glaucoma or ocular hypertension.

Methods: This was a randomized, double-masked study with two parallel groups and a treatment period of 6 months. The primary objective of the study is to compare the IOP-reducing effect of latanoprost with that of timolol at the end of the 6-month treatment period. A total of 294 patients were included: 149 were in the latanoprost group and 145 were in the timolol group. Latanoprost was administered in the evening.

Results: Diurnal IOP (9:00 AM, 1:00 PM, 5:00 PM) was reduced from 25.2 to 16.7 mmHg (33.7%) with latanoprost and from 25.4 to 17.1 mmHg (32.7%) with timolol as determined at the end of the 6-month treatment period. No upward drift in IOP occurred with either drug during the treatment period. Latanoprost caused somewhat more conjunctival hyperemia than timolol and more corneal punctate epithelial erosions. However, both drugs were generally well tolerated. The most significant side effect of latanoprost was increased pigmentation of the iris which was observed in 15 patients (10.1%). Timolol caused more systemic side effects than latanoprost.

Conclusions: Latanoprost 0.005% administered once daily in the evening reduced IOP at least as well as timolol 0.5% administered twice daily. Latanoprost was generally well tolerated systemically and in the eye. However, the drug has an unusual side effect of increasing the pigmentation of the iris, particularly in individuals with green-brown or blue-brown eyes. *Ophthalmology 1996;103:126–137*

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Latanoprost (known previously as PhXA41) is a new prostaglandin analogue developed to reduce the intraocular pressure (IOP) in treating glaucoma. Latanoprost is a selective FP receptor (prostaglandin $F_{2\alpha}$ receptor [$PGF_{2\alpha}$]) agonist which has an improved therapeutic index in the eye when compared with the $PGF_{2\alpha}$-isopropyl ester analogue previously reported.[1–3] Several phase II clinical trials have demonstrated that latanoprost is effective and well tolerated in patients with a long duration of action.[4–10]

Prostaglandin $F_{2\alpha}$ and latanoprost have an interesting mode of action, in that they increase the uveoscleral outflow of aqueous humor in primates.[11–14] In this outflow pathway, the aqueous humor percolates through the ciliary muscle, suprachoroidal space, and the sclera instead of exiting the eye through the trabecular meshwork and

Schlemm canal. In humans, latanoprost also has been shown to increase the uveoscleral outflow,[15] in addition to causing a slight increase in outflow facility.[16] Latanoprost has not been found to exert any significant effect on aqueous humor production.[15,16]

The purpose of the current study is to compare the IOP-reducing effect and side effects of 0.005% latanoprost administered once daily in the evening with 0.5% timolol (Timoptic) administered twice daily during long-term treatment in a large patient population. In long-term toxicity studies, both naturally occurring and synthetic prostaglandins have been shown to induce increased pigmentation of the iris in monkeys (unpublished data, Pharmacia, Uppsala, Sweden); therefore, en face and iris color photographs have been taken at regular intervals of all patients throughout the study period.

Patients and Methods

Patients

A total of 294 patients with open-angle glaucoma or ocular hypertension were included in the study. The study was approved by the Medicines Control Agency and the Hospital Ethics Committee of each center participating in the study. All patients signed an informed consent form after receiving detailed information about the study. The patients were informed about the possible risk of increased iris pigmentation. Patients of either sex, at least 40 years of age with unilateral or bilateral primary open-angle glaucoma, exfoliation glaucoma, pigmentary glaucoma, or ocular hypertension with IOP of 22 mmHg or higher, measured during the prestudy period, were eligible for the study. If only one eye was eligible but both eyes needed treatment, patients were not included. Patients with newly diagnosed glaucoma or ocular hypertension were preferred. However, patients with established glaucoma also were included, but if they had received glaucoma medication, the following washout periods were employed: 2 weeks for adrenergic agonists and 5 days for cholinergic agonists and oral carbonic anhydrase inhibitors. Patients who had been treated with topical beta-blockers within 6 months of study start or at any time for a period longer than 3 months were not included. Treatment with systemic beta-blockers was accepted on the condition that no change would take place during the study period.

Excluded were patients who had a history of acute angle closure, severe ocular trauma at any time, or had undergone intraocular surgery or argon laser trabeculoplasty within 6 months of the start of the study. Patients with a history of severe dry eye syndrome, or those who had had ocular inflammation or infection within 3 months of the start of the study, and patients using contact lenses also were excluded.

Normal routines for prescribing topical beta-blockers were followed, thus excluding patients with cardiac failure, sinus bradycardia, second- and third-degree atrioventricular block, a history of actual bronchial asthma, or chronic obstructive lung disease. Women of childbearing potential and nursing mothers were excluded, as were patients in whom it was believed that one drug alone was not likely to be sufficient to reduce the IOP sufficiently to preserve the function of the optic nerve head and/or visual fields.

Examination Schedule and Procedures

The schedule of examinations and procedures is presented in Table 1. During the month preceding the start of the study (baseline day), patients were assessed for eligibility and examined according to the schedule in Table 1. During the treatment period of 6 months, there were six visits scheduled, starting with the baseline visit. The remaining visits took place 2, 6, 12, 18, and 26 weeks after the baseline visit. The baseline visit and the last visit were entire-day visits, including examinations at 9:00 AM, 1:00 PM, and 5:00 PM, whereas the other visits included an examination at 9:00 AM only (Table 1).

At the prestudy visit, a medical and ocular history was taken, and gonioscopy was carried out unless previously performed. Two prestudy visual fields had to be obtained: one within 6 months of study start and the other during the prestudy period. Biomicroscopy and ophthalmoscopy were performed, and IOP and Snellen visual acuity were measured. In addition, the blood pressure and heart rate were determined, en face and iris photographs were taken, and urine and blood samples were collected. At the prestudy visit, any ocular and systemic symptoms and conjunctival hyperemia also were assessed. At the last visit, after 6 months of treatment, all the examinations performed during the prestudy visit, including visual fields, were carried out, except gonioscopy.

The different examinations and procedures performed between the prestudy visit and the last visit are shown in Table 1. Iris photography was carried out in addition to the prestudy visit at the 12-, 18-, and 26-week visits. Snellen visual acuity was measured at each visit but the refractive error was determined only at baseline and the last visit unless the visual acuity had changed.

At the baseline visit and the last visit, IOP was measured at 9:00 AM, 1:00 PM, and 5:00 PM, at which times biomicroscopy and an assessment of conjunctival hyperemia also were performed. On all other occasions, the examination was performed only at 9 AM. A deviation of 4 days for visit 2 (2 weeks) and 1 week for the other visits was acceptable. At least 3 hours had to elapse between two consecutive IOP measurements.

At the end of the baseline day and the last visit, the patients were asked about any symptoms that they had had during the day. At the beginning of all visits except the baseline day, the patients were asked whether they had had any symptoms or had been ill since last visit. The symptoms, both ocular and general, were graded as mild, moderate, or severe. Conjunctival hyperemia was graded by comparing the appearance of the bulbar conjunctiva to standard photographs (provided by Pharmacia), illustrating mild, moderate, and severe conjunctival hyperemia. The IOP was measured by Goldmann applanation tonometry. Three consecutive readings were

Table 1. Schedule of Examinations and Procedures

Examinations	Prestudy −4 Wks	Visit 1 Day 0			Visit 2 Day 14 ±4 Days	Visit 3 Week 6 ±1 Week	Visit 4 Week 12 ±1 Week	Visit 5 Week 18 ±1 Week	Visit 6 Week 26 ±1 Week		
		9 AM	1 PM	5 PM	9 AM	9 AM	9 AM	9 AM	9 AM	1 PM	5 PM
Medical and ocular history	X										
Gonioscopy	X										
Visual fields	X									X	
Ophthalmoscopy	X										X
Symptomatology	X			X	X	X	X	X	X		X
Visual acuity	X	X			X	X	X	X	X		
Refraction		X							X		
Slit-lamp examination	X	X	X	X	X	X	X	X	X	X	X
Conjunctival hyperemia	X	X	X	X	X	X	X	X	X	X	X
Intraocular pressure	X	X	X	X	X	X	X	X	X	X	X
Photography (iris)	X						X	X	X		
Photography (en face)	X								X		
Blood pressure	X	X			X		X		X		
Heart rate	X	X			X		X		X		
Blood sample	X								X		
Urine sample	X								X		

taken at each time, and the mean of the three values was used in the statistical analyses. The diurnal (day time) IOP was calculated as the average of the 9:00 AM, 1:00 PM, and 5:00 PM measurements. Aqueous flare was investigated carefully, but fluorescein flare was not reported. Any cells present in the aqueous humor were counted in a slit of approximately 2 mm. The blood pressure was measured by ordinary sphygmomanometry in the brachial artery with the patient in the sitting position, and the heart rate was determined on the same occasion. The patients had to rest for 10 minutes before the measurement.

Blood and urine samples were obtained at baseline and at the last visit. The following tests were performed: hematology—hematocrit, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, erythrocytes, leukocytes, differential count, platelets, prothrombin, and activated partial thromboplastin time; blood chemistry—total cholesterol, high- and low-density lipoprotein fractions, triglycerides, total protein, creatinine, urea, bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, Na^+, K^+, Ca^{++}, and Cl^-; and urinalysis—protein and glucose. The analysis of the samples was performed in the local hospital laboratory, and the reference values of each laboratory were used.

The iris color was assessed by the investigators and described as blue/gray/green, hazel, or brown. During the course of the study, a change in iris color developed in some patients. This prompted the use of a more precise classification of iris color, and the following classification system was adopted: (1) blue or gray, (2) blue or gray with slight yellow or brownish areas around the pupil, (3) blue or gray with distinct brown areas mostly around the pupil, (4) green, (5) green with slight yellow or brownish around the pupil, (6) green with distinct brown areas mostly around the pupil, (7) brown (white patients), (8) brown with lighter or yellowish areas peripherally, (9) brown (black patients).

Treatment Schedule

All patients were provided with two clearly labeled dropper bottles, one for morning treatment and one for evening treatment. The patients who were randomized to latanoprost treatment received the drug in the evening and placebo (vehicle of latanoprost eye drops) in the morning. Patients who were randomized to timolol received active drug in the morning and the evening. The patients were instructed to instill the medication at approximately 8:00 AM and 8:00 PM. On visit days to the clinic, the eye drops to be administered in the morning were instilled at the clinic after the 9:00 AM examination. Thus, approximately 13 hours elapsed between administration of the study drugs and the IOP measurement in the morning. The first eye drop was instilled at 8:00 PM on the baseline day and the last after the 9:00 AM examination of the last visit. At the last visit, patients were given the opportunity to continue directly with the latanoprost treatment in an open-label study, the results of which will be presented separately.

Study Design and Statistical Analysis

The study was designed as a randomized double-masked parallel group comparison of latanoprost and timolol. Fourteen centers in United Kingdom participated in the study. The patients were allocated to different treatment groups according to a pregenerated randomization list. Randomization was stratified per center and performed in blocks for each center. The sample size was

Table 2. Patients Withdrawn from Treatment

Case No.	Time of Withdrawal	Treatment Group	Reason
104	Week 12	Latanoprost	Prescription of atenolol due to chest pain
406	Week 6	Latanoprost	Blurred vision, photophobia, tearing, eye pain, punctate epithelial erosions, hyperemia
408	Week 9	Latanoprost	Patient uncontactable
517	Week 12	Latanoprost	Patient uncontactable
701	Week 19	Latanoprost	Bad compliance
702	Week 11	Latanoprost	IOP not controlled
708	Week 4	Latanoprost	IOP not controlled
714	Week 7	Latanoprost	Eye pain, redness, stinging, watering
724	Week 18	Latanoprost	Unable to attend clinic
928	Week 2	Latanoprost	Nonattendance
1409	Week 26	Latanoprost	Patient busy; withdrawal after morning session
1518	Week 6	Latanoprost	Shortness of breath
106	Week 2	Timolol	Low blood pressure
127	Week 18	Timolol	Breathing problems
210	Week 3	Timolol	Allergic conjunctivitis
217	Week 12	Timolol	General lassitude and various ocular symptoms
402	Week 13	Timolol	Wheezing, dyspnea
512	Week 12	Timolol	Eyelid and periorbital edema
712	Week 6	Timolol	Headaches
910	Week 2	Timolol	Previously received Timoptol
919	Week 8	Timolol	Headaches
926	Day 2	Timolol	Self-withdrawal
1109	Week 2	Timolol	Ocular allergic reaction
1402	Day 1	Timolol	Ocular allergeric reaction
1403	Week 12	Timolol	Low blood pressure and slow pulse rate
1510	Week 18	Timolol	Productive cough

IOP = intraocular pressure.

based on the assumption that the true diurnal reduction in IOP was at the most 0.5 mmHg better in patients treated with timolol than in patients treated with latanoprost at the end of a 6-month treatment. Constructing a two-sided 90% confidence interval for the difference in diurnal IOP reduction (latanoprost–timolol), which is below 1.5 mmHg in favor of timolol, with a probability of 0.80 and a standard deviation for the mean reduction in diurnal IOP of 3 mmHg, resulted in a sample size of 111 patients per group. To compensate for withdrawals and drop-outs, 149 and 145 patients per group were included. If both eyes were treated, the mean IOP of the two eyes was used.

A parallel design was used to test whether latanoprost had a comparable IOP-reducing effect to timolol. Analysis of covariance (treatment group and center as factors and baseline IOP as covariate and their interactions) was used. The model then was reduced to include only the factors and the covariate. A 90% confidence interval was constructed for the difference in diurnal IOP reduction. The diurnal IOP change from baseline was used in the analysis. The results are presented as the mean ± standard deviation.

Withdrawal of Patients and Protocol Deviations

Twelve patients in the latanoprost group and 14 patients in the timolol group were withdrawn during the course of the study for reasons specified in Table 2. In addition, protocol deviations occurred. However, these were distributed fairly evenly between the groups and did not affect the statistical analyses of the results. One patient was not 40 years of age at inclusion. Decisions concerning how protocol deviations would be dealt with in the statistical analyses were made before the code was broken.

Study Drugs

Latanoprost (13,14-dihydro-17-phenyl-18,19,20-trinor-$PGF_{2\alpha}$-isopropyl ester) provided by Pharmacia was used at a concentration of 0.005% (50 μg/ml). The solution contains 0.02% benzalkonium chloride as preservative. The placebo drops contained the vehicle of the latanoprost eye drops, including the same amount of benzalkonium chloride. Timolol 0.5% eye drops were refilled in identical bottles to those of latanoprost and placebo. The stability of the timolol eye drops in the latanoprost eye drop dispenser was investigated before the study and was found to be adequate. The bottles of the latanoprost, placebo, and timolol eye drops were labeled identically and were identical in appearance.

Results

The demographic characteristics of the treatment groups are presented in Table 3. The randomization was successful with a fairly even distribution of sex, age, race, and disease between the treatment groups.

Intraocular Pressure

The effect of latanoprost and timolol on IOP is shown in Figure 1 and Table 4. Latanoprost reduced the diurnal IOP from a baseline level of 25.2 ± 3.4 mmHg to 16.7 ± 2.6 mmHg ($P < 0.0001$) at the end of the treatment period. The corresponding figures for IOP with timolol were 25.4 ± 3.6 mmHg and 17.1 ± 2.6 mmHg ($P < 0.0001$). The drugs can be considered equally effective, although latanoprost tended to be somewhat better as documented at

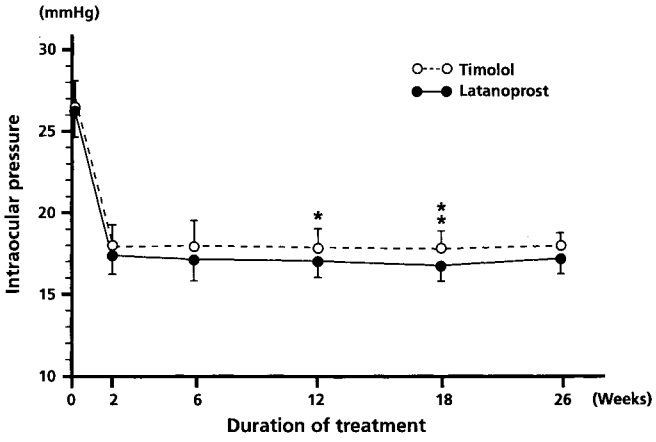


Figure 1. Intraocular pressure response to latanoprost and timolol during the course of the study (9:00 AM measurements, 13 hours after drug was administered). Mean ± standard deviation. Asterisk = $P < 0.05$; double asterisk = $P < 0.02$.

9:00 AM at the 12- and 18-week visits. The difference in IOP reduction at those times was 0.4 mmHg ($P = 0.04$) and 0.9 mmHg ($P < 0.001$), respectively, in favor of latanoprost (Fig 1, Table 4). However, at the last visit, there was no statistically significant difference in the IOP reduction from baseline between latanoprost and timolol. An upward drift in IOP during the treatment period was not seen with either drug (Fig 1). The reduction of IOP at the end of the study was 33.7% in the latanoprost group and 32.7% in the timolol group compared with baseline.

Latanoprost reduced IOP equally as well in men as in women, and no difference in the response between patients with open-angle glaucoma or ocular hypertension was observed. No difference in response to latanoprost was

Table 3. Demographic Characteristics of Study Population

Variable	Latanoprost	Timolol	Total
Men	98	93	191
Women	51	52	103
Total no. of patients	149	145	294
Age (yrs)			
Mean ± SD	64.7 ± 9.5	65.3 ± 10.5	65.0 ± 10.0
Range	41-85	39-88	39-88
Race			
White	143	142	285
Black	6	3	9
Unilateral treatment	27	13	40
Bilateral treatment	122	132	254
Primary open-angle glaucoma	59	62	121
Exfoliation glaucoma	3	2	5
Pigmentary glaucoma	2	1	3
Ocular hyptertension	80	68	148
Mixed type of glaucoma*	5	12	17

SD = standard deviation.
* Including ocular hypertension.

Table 4. Intraocular Pressure Measured during the Study*

	0 Wk			2 Wks	6 Wks	12 Wks	18 Wks	26 Wks		
	9 AM	1 PM	5 PM	9 AM	9 AM	9 AM	9 AM	9 AM	1 PM	5 PM
Latanoprost (mmHg)										
Mean ± SD	26.2 ± 3.6	24.9 ± 3.9	24.6 ± 3.8	17.4 ± 2.9	17.2 ± 3.2	17.1 ± 2.9	16.7 ± 2.5	17.1 ± 2.8	16.5 ± 2.8	16.5 ± 2.7
No.	149	149	149	127	128	130	130	137	133	133
Timolol (mmHg)										
Mean ± SD	26.5 ± 3.9	24.9 ± 3.9	24.8 ± 4.0	17.8 ± 2.6	17.5 ± 2.7	17.8 ± 2.8	17.7 ± 2.8	17.7 ± 2.8	16.6 ± 2.8	17.1 ± 3.0
No.	145	145	145	119	120	125	128	131	129	129

SD = standard deviation.

* Due to protocol deviations and withdrawals the mean intraocular pressure at different time points is not based on all patients.

observed when the patient population was stratified for age. Thus, it would seem that latanoprost reduces IOP uniformly, independent of sex, age, or type of glaucoma. However, there was a small but significant ($P = 0.006$) difference in IOP response between patients with blue/green/gray eyes (8.0 ± 2.7 mmHg) and patients with hazel eyes (9.3 ± 3.0 mmHg), but not between patients with blue and brown eyes. Males responded significantly ($P < 0.01$) better than females to timolol (reduction in IOP, 9.0 ± 3.5 mmHg and 7.1 ± 3.0 mmHg, respectively), and patients with primary open-angle glaucoma responded significantly ($P < 0.01$) better than patients with ocular hypertension to timolol (reduction in IOP, 9.4 ± 3.8 mmHg and 7.1 ± 2.8 mmHg, respectively).

Conjunctival Hyperemia

Latanoprost caused statistically significantly ($P < 0.001$) more conjunctival hyperemia than timolol. However, the degree of hyperemia was very slight as can be seen in Figure 2. Analysis of the degree of increase in maximum conjunctival hyperemia at the last visit compared with maximum hyperemia during baseline shows that 63.8% of the patients treated with latanoprost and 81.7% of the patients treated with timolol had no increase in hyperemia (Table 5). A total of 26.1% of the patients treated with latanoprost and 17.6% of the patients treated with timolol had a barely detectable increase in hyperemia compared with baseline and only 2.9% of the patients treated with latanoprost had a mild to moderate increase in hyperemia (Table 5). Thus, 89.9% of the patients treated with latanoprost had no or barely detectable hyperemia compared with baseline.

Blood Pressure and Heart Rate

Neither latanoprost nor timolol had any consistent effect on systolic or diastolic blood pressure as measured 13 hours after administration of the drugs, although there was a general tendency toward a slight decrease in blood pressure with time. However, timolol slightly but statistically significantly ($P = 0.02$) reduced the heart rate from a baseline value of 73.8 ± 11.6 beats/minute to 71.8 ± 10.9 beats/minute at the last visit.

Biomicroscopy, Visual Acuity, and Visual Fields

Neither latanoprost nor timolol caused significant aqueous flare or infiltration of cells into the aqueous humor. In one patient in the latanoprost group, between three and six cells were detected in the aqueous humor on two occasions. In another patient, slight flare was detected once and cells (2) another time. In one patient of the timolol group, cells (7) were detected in the aqueous humor once. Neither visual acuity nor refraction were affected by latanoprost or timolol, nor was any clear-cut effect noted on visual fields. However, one patient in the timolol group had a deterioration in the visual field during the study period.

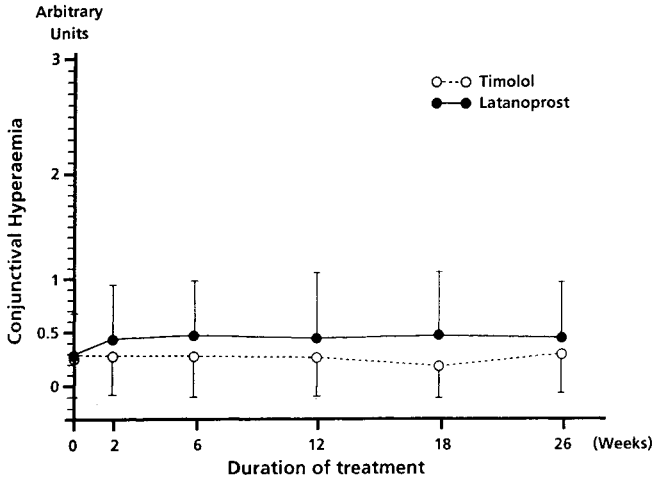


Figure 2. Conjunctival hyperemia registered at 9:00 AM during the course of the study. There was a significant ($P < 0.001$) difference in hyperemia between latanoprost and timolol throughout the treatment period. Mean ± standard deviation.

Withdrawals and Side Effects

The patients withdrawn from the study are specified in Table 2. Patients were withdrawn from the latanoprost group due to inadequate IOP control (n = 2); local side effects such as hyperemia, corneal punctate epithelial erosions and eye pain (n = 2); and shortness of breath (n = 1). In the timolol group, patients were withdrawn due to breathing problems (n = 2), arterial hypotension/bradycardia (n = 2), headaches (n = 2), and ocular allergic reactions (not confirmed as drug related) (n = 2).

The ocular findings and symptoms reported during the treatment period are presented in Table 6. It can be seen that more ocular symptoms such as foreign body sensation, stinging, conjunctival hyperemia, itching, and burning occurred in the latanoprost group than in the timolol group. Punctate epithelial erosions also were more frequent in the latanoprost group. Except for one patients whose visual field deteriorated (timolol), and several patients with increased pigmentation of the iris (latanoprost), none of the symptoms and findings were considered important, although several were reported as adverse events. Overall, both drugs were fairly well tolerated in the eye.

The systemic findings and symptoms reported during the treatment period are presented in Table 7. With the exception of findings and symptoms that can be considered as incidental (e.g., infections), more systemic side effects were reported in the timolol group. Thus, there were more patients with headache, shortness of breath, bronchitis, arterial hypotension, pain, and lassitude in the timolol group. In a few patients, deviating blood or urine test results were reported as adverse events. Although the results of several of the blood and urine tests were outside the reference values as can be anticipated statistically, there were only a few marked deviations, and these were not considered to be related to the study drugs. Overall, both drugs were well tolerated.

Four serious adverse events occurred during treatment with latanoprost. These included one patient with angina

Table 5. Increase in Maximum Conjunctival Hyperemia versus Baseline Determined at the Last Visit

	No. of Patients	(%)
Latanoprost*		
No increase	88	(63.8)
Barely detectable (0.5)	36	(26.1)
Mild (1.0)	10	(7.2)
Mild-moderate (1.5)	4	(2.9)
Timolol		
No increase	107	(81.7)
Barely detectable (0.5)	23	(17.6)
Mild (1.0)	1	(0.8)
Mild-moderate (1.5)	0	(0)

* Values in parentheses indicate units above baseline hyperemia.

Table 6. Number of Patients with Ocular Findings and Symptoms Reported during a 6-month Treatment with Latanoprost and Timolol*

Ocular Side Effect	Latanoprost	Timolol
Foreign body sensation	33 (10)	11 (3)
Stinging	25 (3)	21 (1)
Conjunctival hyperemia	22 (14)	9 (3)
Punctate epithelial erosions	19 (13)	10 (4)
Itching	15 (2)	11 (2)
Blurred vision/vision disturbance	17 (7)	19 (4)
Eye pain/irritation	13 (3)	10 (1)
Tearing	8 (2)	9 (1)
Burning	7 (1)	2 (0)
Eyelid inflammation/discomfort	7 (3)	4 (1)
Ocular discomfort	5 (0)	4 (0)
Eyelid edema/erythema	5 (3)	5 (3)
Discharge	5 (4)	3 (2)
Dry eye	4 (0)	4 (2)
Blepharitis	4 (1)	1 (0)
Conjunctivitis	3 (3)	1 (1)
Photophobia	3 (1)	2 (0)
Increased iridial pigmentation	2 (2)	0
Allergic reaction	0	2 (2)
Visual field deterioration	0	1 (1)
Other†	20 (5)	29 (7)

* Values in parentheses indicate how many were reported as adverse events.

† Including (latanoprost): microcystic epithelial change, sensation of pulsation, corneal limbal infiltrates, posterior vitreous detachment, eyes feel tired; (timolol): retinal neovascularization, periorbital edema, photopsia, discoloration of lower eyelid skin, stye on lower lid, cells in anterior chamber, keratic precipitates.

Table 7. Number of Patients with Systemic Findings and Symptoms Reported during a 6-month Treatment with Latanoprost and Timolol*

Finding/Symptom	Latanoprost	Timolol
Upper respiratory tract infection	24 (8)	15 (7)
Headache	9 (1)	14 (4)
Pain (muscle, joint, back)	6 (2)	11 (2)
Bronchitits	5 (2)	5 (3)
Lassitude	2 (1)	6 (1)
Shortness of breath/wheezing	2 (2)	5 (3)
Arterial hypotension	0	2 (2)
Other†	41 (18)	45 (27)

* Values in parentheses indicate how many were reported as adverse events.

† Including (latanoprost/timolol): cough (1/3), peripheral edema (2/2), angina pectoris (1/1), abdominal pain-discomfort (0/3), gastric flu-diarrhea (2/1), ear infection-discomfort (4/2), dermatitis (1/1), tingling (2/0), nausea (1/0), dizziness-vertigo (2/3), depression (1/0), other (12/17).

pectoris, one with myocardial infarction, one with external carotid stenosis, and one with retinal detachment. In the timolol group, five serious adverse events were reported. These included one patient with cerebrovascular accident, one with herpes zoster, one with bronchitis, one with hematemesis, and one with renal colic. None of these events were reported to be related to the use of study drug.

Increased Pigmentation of the Iris

Of the 149 patients treated with latanoprost, increased pigmentation of the iris developed in 15 (10.1%) (Table 8). None of the patients treated with timolol had this side effect. In only two of the patients was the change in iris pigmentation regarded as definite and reported as an adverse event; the remaining patients were considered as having a suspicious increase in pigmentation. The earliest sign of increased pigmentation was detected at 12 weeks, but most often the change became suspect at weeks 18 to 26 weeks. Typical cases of increased pigmentation of the iris are displayed in Figures 3 to 5. In all patients in whom clear-cut increased pigmentation of the iris was identified, the treatment was terminated, and the patients entered a follow-up recovery program.

Discussion

The concept of using prostaglandins as IOP-lowering drugs for glaucoma treatment is fairly recent and unparalleled.[17,18] Several advantages can be presented for using prostaglandins as IOP-reducing agents. Prostaglandins enhance the uveoscleral outflow,[11-15] which may be a way of circumventing the trabecular outflow, which is blocked in glaucoma. In addition, prostaglandins undergo little metabolism in the eye, but once they have entered the general circulation they are rapidly metabolized and excreted. Thus, when applied topically the prostaglandins can be regarded as oculoselective, and systemic side effects should not occur. Despite the good IOP-reducing effect of many prostaglandins, their use has been hampered by the local side effects in the eye. These side effects typically comprise conjunctival hyperemia and superficial irritation of the eye.[19] Latanoprost, a synthetic prostaglandin analogue, is a selective FP receptor agonist and had a considerably better side-effect profile in the eye than $PGF_{2\alpha}$-isopropyl ester, for example.[3,20] In phase II clinical trials, latanoprost has been effective and well tolerated.

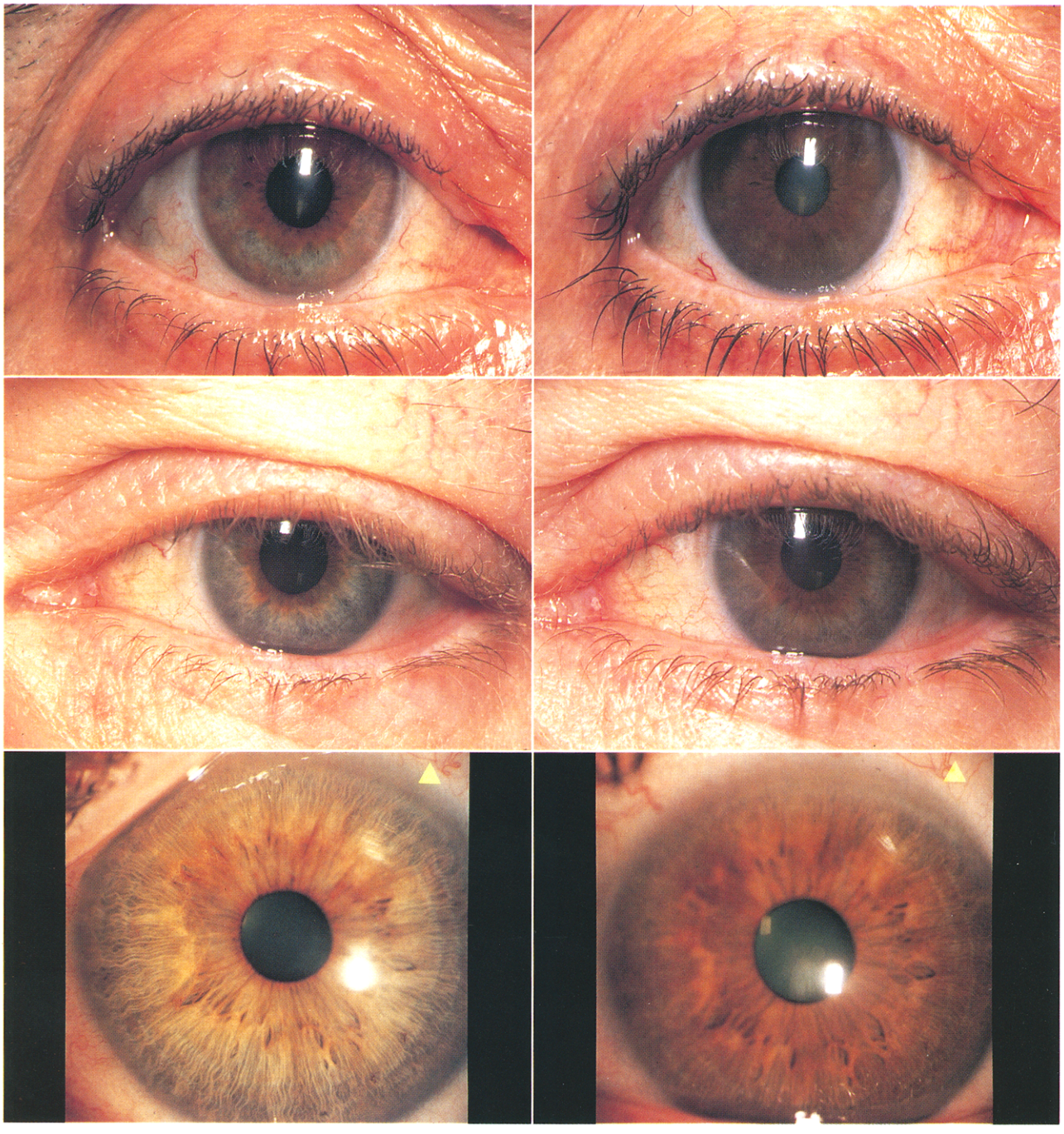
From previous short-term studies with latanoprost and PhXA34, an epimeric mixture containing latanoprost, it is obvious that the peak in IOP-reducing effect of latanoprost is reached 8 to 12 hours after the drug has been administered,[7,8,21,22] and administering latanoprost twice daily does not improve the effect on diurnal IOP.[10] Timolol is recommended mostly to be administered twice daily; thus, the IOP values obtained 12 to 13 hours after the drug has been administered can be considered representative of trough values. However, it has been demonstrated that the duration of action of 0.5% timolol eye drops is considerably longer than 12 hours and can be administered once daily.[23,24] Thus, it is reasonable to assume that the diurnal IOP values based on readings at 13, 17, and 21 hours after latanoprost is given and 4, 8, and 13 hours after timolol is given during long-term maintenance therapy are comparable vis-a-vis the peak-trough effect.

Both latanoprost and timolol caused a marked and sustained reduction in IOP throughout the study period

Table 8. Patients with Increased Iridial Pigmentation*

Case No.	Weeks of Treatment	Eye Color (before treatment)
117	12	Green-brown (hazel)
118	18	Green-brown (blue/green/gray)
120	18	Green-brown (hazel)
212	26	Green-brown (brown)
213	12	Blue/gray-brown (brown)
219	12	Green-brown (hazel)
501	26	Green-brown (brown)
510	12	Green-brown (brown)
610	18	Green-brown (hazel)
611	18	Green-brown (brown)
725	12	Blue/gray-brown (blue/green/gray)
1207	26	Green-brown (hazel)
1406	12	Green-brown (hazel)
1503	26	Blue/gray-brown (brown)
1519	26	Green-brown (hazel)

* The visit at which the first sign or suspicion of increased pigmentation occurred is also indicated. Eye color as assessed by investigator is in parentheses.



Top, Figure 3. Green-brown iris before **(left)** and after **(right)** 6-month treatment.

Center, Figure 4. Blue/gray-brown iris with typical brown ring around the pupil before **(left)** and after **(right)** 6-month treatment.

Bottom, Figure 5. Green-brown iris before **(left)** and after **(right)** 6-month treatment.

of 6 months. The IOP reduction was approximately the same magnitude as that seen in short-term clinical trials with latanoprost.[5,6,8–10,15,16] Being administered at a concentration of only 0.005% once daily, latanoprost must be considered a remarkably potent and efficacious drug. Because IOP at 5:00 PM (21 hours after dosage) was not higher than that measured at 9:00 AM or 1:00 PM, it is obvious that the duration of action of latanoprost is at least 21 hours and most likely up to 24 hours.

There was no statistically significant difference in the IOP reduction between latanoprost and timolol at 6 months, but latanoprost was more effective at 3 and 4.5 months of treatment. However, it should be noted that this difference is based on 9:00 AM IOP values obtained

approximately 13 hours after administration of the study drugs, and they can be regarded as trough values for timolol and peak values for latanoprost. On the other hand, as noted above, it is well known and documented in the literature that 0.5% timolol has a duration of action far beyond 12 hours.[23,24] The possibility that the placebo drop would have increased the IOP-reducing effect by enhancing the penetration of latanoprost through the cornea can be excluded because the placebo drop was given 12 hours before the latanoprost drop. It is very unlikely that there would be some drug penetration-enhancing effect 12 hours after administration of benzalkonium chloride (placebo). We can conclude that during the period of this study (1) the drugs were equally effective or (2) latanoprost was marginally more effective. Importantly, no sign of tachyphylaxis or upward drift of IOP was observed in patients treated with latanoprost. With latanoprost or PhXA34, the epimeric mixture containing latanoprost, no increase in IOP has been detected during the first hours after administration of the drugs,[7,8,22,25,26] as has been shown (e.g., for $PGF_{2\alpha}$-isopropyl ester).[19] Thus, it is most unlikely that a prostaglandin-induced increase in IOP would have been missed, because latanoprost only reduces IOP.

Previous studies have demonstrated that latanoprost induces significantly less conjunctival hyperemia than $PGF_{2\alpha}$-isopropyl ester.[4–10] The current study supports this because in approximately 90% of the patients either no increase or only a barely detectable increase in hyperemia could be detected. A mild increase in conjunctival hyperemia was registered in 7% of the patients and a mild to moderate increase in 3%. Thus, although latanoprost does cause conjunctival hyperemia in some individuals, it is a cosmetic problem for only a few. It may be argued that maximum hyperemia occurs during sleep because latanoprost was administered in the evening. This is, however, unlikely because it has been shown in a recent study comparing morning administration and evening administration of latanoprost that there is no difference in hyperemia 0 to 8 hours and 12 to 20 hours after the drug is administered. Neither was there any significant fluctuation in conjunctival hyperemia during the first 8 hours after administration of latanoprost.[25]

Prostaglandins have been demonstrated in numerous studies to induce a breakdown of the blood–aqueous barrier and to cause signs of inflammation in animals, particularly in rabbits.[27–29] However, this effect has not been demonstrated in primates.[27–30] Neither has it been seen in humans during short-term therapy with $PGF_{2\alpha}$-isopropyl ester.[19,20] Thus, there is a marked species difference with respect to this effect. Except for two patients in the latanoprost group and one in the timolol group, aqueous flare or cells could not be detected during treatment. Thus, it can be concluded that latanoprost has no measurable effect on the blood–aqueous barrier, and does not induce changes associated with inflammation. This result is in good agreement with the results of previous studies in which the integrity of the blood–aqueous barrier during latanoprost treatment has been studied using fluorophotometry[16] or with laser flare meter.[7,8]

Neither visual acuity nor refractive error was affected by latanoprost or timolol. No changes could be detected in the cup:disc ratio or the visual fields, which may be anticipated because the duration of the study was only 6 months in duration. One patient in the timolol group had deterioration of the visual field but this was considered incidental.

Both timolol and latanoprost were well tolerated in the eye, but latanoprost caused more subjective and objective side effects. In particular, the punctate epithelial erosions of the cornea were more frequent in the latanoprost group. It is important to note that in the latanoprost group a placebo drop had to be administered in the morning to mask the study since timolol was administered twice daily. The latanoprost and placebo eye drops contained 0.02% benzalkonium chloride and the timolol eye drops contained only 0.01% benzalkonium chloride, thus twice as much preservative was administered to the patients in the latanoprost group. It is well known that benzalkonium chloride has an irritating effect on the surface of the eye, causing punctate epithelial erosions; therefore, it can be anticipated that when the latanoprost eye drops are used once daily less punctate keratopathy will occur. In most patients, the punctate epithelial erosions were mild and without clinical significance. It may be argued that punctate epithelial erosion may have occurred during sleep because latanoprost was administered in the evening and thus the figures presented underestimate the true rate of this side effect. However, this is unlikely as no difference in the rate of punctate keratopathy was seen in another study in which the effect and side effects of latanoprost administered in the morning or the evening were compared.[25] The excess preservative used due to the placebo drop also may have contributed to some of the other local side effects, including the conjunctival hyperemia, although it could be argued that a placebo drop may have a relieving effect on the eye, thus reducing the number of side effects. However, the latter possibility seems remote because there was no significant difference in frequency of ocular side effects between morning and evening administration of latanoprost in another study, in which a placebo drop was used in the morning.[25]

Timolol caused more systemic side effects than latanoprost. Patients in whom timolol treatment was contraindicated were not included in the study. Yet, despite this restriction approximately 4.8% of the patients included in the timolol group reported side effects related to the respiratory or cardiovascular system in contrast to 1.3% in the latanoprost group. Twenty (13.8%) patients in the timolol group reported headache or lassitude compared with 11 (7.4%) in the latanoprost group. Timolol also reduced the heart rate as measured 13 hours after administration of the drug.

Increased pigmentation of the iris was seen in 15 patients in the latanoprost group. Of these, only two were regarded as definite and reported as adverse events, the rest were considered suspicious of having increased pigmentation. Two patients in the timolol group also had suspect increased pigmentation of the iris. These were later found to be false, indicating that the number of patients

in the latanoprost group who might have increased pigmentation may be slightly overestimated. All such patients in the latanoprost group have been regarded as having a mild increase in pigmentation of the iris, and, thus, a worst case figure is presented. It is of particular interest that in patients with pure blue, gray, or brown irides no change in pigmentation was found. Increased pigmentation was seen only in irides with mixed color at baseline, typically green-brown or blue/gray-brown. Frequently, blue, gray or green irides have a brownish or even dark-brown ring around the pupil 1 to 2 mm wide and this may start to spread concentrically. Another type of change in pigmentation was seen in irides with a patchy heterochromatic appearance at baseline. In such irides, the less-pigmented patches, often greenish in appearance, tended to become pigmented, turning brown. Many patients had freckles and nevi in the iris but these did not change during latanoprost treatment.

Increased pigmentation of the iris as a pharmacologic phenomenon, as far as we know, has not been described previously. An extensive preclinical program has been performed to investigate the mechanism of the phenomenon. Both in studies on cultured human iridial melanocytes and on monkeys in vivo there have been no findings that indicate that latanoprost or $PGF_{2\alpha}$ would promote proliferation of iridial melanocytes (unpublished data, Pharmacia). Therefore, the most likely explanation is a prostaglandin-induced stimulation of melanin formation in the iridial melanocytes. In monkeys with yellowish-greenish eyes, a fairly similar path in pigmentation has occurred (i.e., manifest pigmentation, depending on dose, was seen after 3–12 months of topical treatment with prostaglandin).

Obviously, the practical consequences and the mechanism of increased pigmentation of the iris must be scrutinized before latanoprost can reach a widespread clinical use. The longest follow-up of the recovery of increased pigmentation currently is approximately 1 year. We have not seen any indications that either the pigmentation continues to increase after treatment has been stopped or the changes are reversible. In contrast to dermal melanocytes, iridial melanocytes have been described as "continent melanocytes,"[31] which do not release the pigment granules or donate them to neighboring cells and therefore the color change of the iris is unlikely to be reversible or at the best it is slowly reversible. This also means that pigment dispersion to the rest of the eye or trabecular meshwork is unlikely. No increase in deposition of pigment in the chamber angle by gonioscopy has been noted in patients with increased iris pigmentation.

Appendix

The Latanoprost Study Group in United Kingdom:

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