Comparison of Latanoprost and Timolol in Patients with Ocular Hypertension and Glaucoma

A Six-month, Masked, Multicenter Trial in the United States

*Carl B. Camras, MD, the United States Latanoprost Study Group**

Purpose: Latanoprost, a new prostaglandin analogue, was compared with timolol for ocular hypotensive efficacy and side effects.

Methods: In a multicenter, randomized, double-masked, parallel group study, 268 patients with ocular hypertension or early primary open-angle glaucoma received either 0.005% latanoprost once daily or 0.5% timolol twice daily for 6 months. All except ten patients from each group successfully completed the study.

Results: Intraocular pressure (IOP) was significantly ($P < 0.001$) reduced and maintained by both medications without evidence of a long-term drift over 6 months. Comparing 6-month with baseline diurnal IOP values, the IOP reduction (mean ± standard deviation) achieved with latanoprost (−6.7 ± 3.4 mmHg) was significantly ($P < 0.001$) greater than that produced with timolol (−4.9 ± 2.9 mmHg). Four patients treated with timolol and none treated with latanoprost were withdrawn from the study because of inadequate IOP control. Pulse rate was significantly reduced with timolol, but not with latanoprost. Slightly more conjunctival hyperemia appeared in latanoprost-treated compared with timolol-treated eyes. Fewer subjective side effects occurred in latanoprost-treated eyes. Both eyes of a patient with a characteristic, concentric iris heterochromia (darker centrally) at baseline showed a definite, photographically documented increase in pigmentation during latanoprost treatment, making the irides uniformly darker. Three additional patients treated with latanoprost were suspects for this color change. Otherwise, no significant difference between treatment groups occurred in visual acuity, slit-lamp examination, blood pressure, and laboratory values.

Conclusion: Latanoprost has the potential for becoming a new first-line treatment for glaucoma *Ophthalmology 1996;103:138–147*

Originally received: October 27, 1994.
Revision accepted: August 31, 1995.

From the Department of Ophthalmology, University of Nebraska Medical Center, Omaha.

* Members of the United States Latanoprost Study Group are listed in the Appendix at the end of this article.

Presented in part at the Glaucoma Society of the International Congress of Ophthalmology in Quebec City, Canada, June 1994, and as a poster at the American Academy of Ophthalmology Annual Meeting, San Francisco, November 1994.

Also submitted for publication, in part, in *Glaucoma Update V*, Krieglstein GK, ed, Springer-Verlag Berlin Heidelberg, which has limited distribution.

Several prostaglandin (PG) prodrugs and analogues are potent, effective, and well-tolerated ocular hypotensive agents in patients with ocular hypertension or glaucoma.[1,2] Of these agents evaluated in clinical trials,[3–23] the 17-

Supported by a grant from Pharmacia Pharmaceuticals, Uppsala, Sweden.

Dr. Camras is a consultant to Pharmacia Ophthalmics, Uppsala, Sweden, and to Alcon Laboratories, Fort Worth, Texas. None of the authors has a proprietary interest in the development or marketing of any drug used in this study or in any competing drug.

Reprint requests to Carl B. Camras, MD, Department of Ophthalmology, University of Nebraska Medical Center, 600 South 42nd St, Omaha, NE 68198-5540.

phenyl-substituted $PGF_{2\alpha}$ analogues apparently provide the greatest separation between ocular hypotensive efficacy and side effects.[8,11,12,15–21,24–26] Previous studies with these analogues have followed only small groups of patients for less than 3 months (Alm et al, unpublished data; presented at the 1993 ARVO Annual Meeting). However, to be useful in treating chronic open-angle glaucoma, it is important to evaluate a drug for efficacy and side effects in large numbers of patients undergoing treatment for extended periods of time. Because nonselective β-adrenergic antagonists are currently the first-line treatment for glaucoma, potentially new therapeutic agents may be compared with β-blockers to establish their relative usefulness in the clinical therapy of glaucoma.

This multicenter, randomized study compares the efficacy and side effects of 0.005% latanoprost (PhXA41; 13,14 - dihydro - 17 - phenyl - 18,19,20 - trinor - $PGF_{2\alpha}$ -1-isopropyl ester) applied topically once daily with 0.5% timolol given twice daily for 6 months to patients with ocular hypertension or glaucoma.

Patients and Methods

Patients

Patients were recruited from 17 centers in the United States. To be eligible for the study, at least one eye of each patient had to meet the following criteria: (1) intraocular pressure (IOP) of at least 22 mmHg with no more than a single ocular hypotensive medication during the screening examination; (2) if only one eye of a patient was eligible for the study, the expectation that the other eye would remain controlled either without treatment or with treatment with the same experimental agent used in the eligible eye; (3) diagnosis of primary open-angle glaucoma, ocular hypertension, exfoliation syndrome, or pigmentary dispersion syndrome; (4) expectation by the investigator that IOP would remain adequately controlled with a single drug treatment for 6 months without optic nerve or visual field progression.

If treated for their elevated IOP, patients discontinued their medication for a minimum of the following intervals before the baseline day: 3 weeks for β-adrenergic antagonists, 2 weeks for adrenergic agonists, and 5 days for cholinergic agonists or carbonic anhydrase inhibitors.

Patients were ineligible for inclusion into the study for any of the following reasons: younger than 40 years of age; currently pregnant, considering pregnancy, or breast feeding; use of any ocular medications other than for glaucoma; diagnosis of any glaucoma type other than specified in the inclusion criteria; advanced glaucoma that would be at risk for progression during the washout period; narrow angles or presence of peripheral anterior synechiae; intraocular surgery or argon laser trabeculoplasty carried out fewer than 6 months before the study; corneal abnormalities or other problems preventing reliable applanation tonometry; inability to temporarily suspend contact lens use for the duration of the study; active eye disease other than ocular hypertension or primary open-angle glaucoma; ocular inflammation less than 3 months before the study; known allergy or contraindication to any medications used in the study (specifically, contraindications to β-blockers, including congestive heart failure, sinus bradycardia, second- or third-degree atrioventricular block, chronic obstructive pulmonary disease, bronchial asthma, etc.); if treated orally with medications known to affect IOP, the expectation that the type or dosage of these drugs would not change during the course of the study; any unstable medical condition; history of noncompliance or unreliability; or inability to adhere to the protocol design.

Protocol

After obtaining appropriate informed consent and approval by the Institutional Review Board at each center, a medical history was taken from each subject, including a list of all systemic medications each was receiving. A complete ophthalmologic history and examination was performed on each patient within 4 weeks of the onset of the study (Table 1).

The protocol used during the 6-month study is described in Table 1. On the baseline day, all of the parameters indicated in Table 1 were assessed. Patients were assigned to treatment by computer-generated randomization, stratified for each center and performed in blocks within each center. Neither the examiners nor the subjects were informed of the identity of the drop received during the course of the study.

Beginning in the evening of the baseline day, one drop (approximately 35 μl) of either 0.005% latanoprost or 0.5% timolol was applied topically to one or both eyes (all eligible eyes) of each of 268 patients. Each patient received two bottles, one carefully labeled for use each morning at 8:00 AM, and the other for the evening at 8:00 PM. The timolol-assigned group of patients received timolol for both doses each day. The latanoprost-assigned group of patients received active latanoprost at 8:00 PM and the vehicle (0.02% benzalkonium chloride, 0.5% monosodium phosphate monohydrate, 0.6% disodium hydrogen phosphate dihydrate, and 0.4% sodium chloride) at 8:00 AM each day. Treatment was continued for 6 months. At 0.5, 1.5, 3, 4.5, and 6 months, the parameters specified in Table 1 were recorded. Patients were told not to take their study medications on the morning of their return visits. After their 8:00 AM examination, their study drops were administered by the study coordinator or by the patient. The treatment code was not broken by the manufacturer until the last patient completed the study and until all case report forms were completed and reviewed for accuracy.

Adverse events were monitored carefully throughout the study. An adverse event was defined as any undesirable event occurring in a subject, regardless if it were considered related to the investigational drug. A serious adverse event was defined as potentially fatal, life threatening, sight threatening, permanently disabling, requiring hospitalization, cancer, or a drug overdose.

Table 1. Timing of Evaluation

Evaluation	Within 4 Wks of Baseline	Baseline			2 Wks	1.5 Mos	3 Mos	4.5 Mos	6 Mos		
		8 AM	12 Noon	4 PM	8 AM	8 AM	8 AM	8 AM	8 AM	12 Noon	4 PM
Visual fields*	X									X	
Subjective side effects†	X	X		X	X	X	X	X	X		X
Conjunctival hyperemia‡	X	X	X	X	X	X	X	X	X	X	X
Slit-lamp biomicroscopy§	X	X	X	X	X	X	X	X	X	X	X
Intraocular pressure‖	X	X	X	X	X	X	X	X	X	X	X
Blood pressure and pulse rate (resting)	X	X			X		X		X		
Color photography of iris	X						X	X	X		
Blood¶ and urine analysis**	X								X		

* Two visual fields (Humphrey 24-2 or 30-2, or Octopus G-1) required within 6 months before baseline day, at least one of which was done within 4 weeks of baseline.

† Blurred vision, photophobia, itching, burning, stinging, tearing, dryness, foreign body sensation, eye pain, and eyelid pain or discomfort.

‡ Based on a relative scale of 0, 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0 by comparing with standard photographs showing no (0), mild (1), moderate (2), and severe (3) hyperemia.

§ Undilated and dilated slit-lamp biomicroscopic examination of the cornea, anterior chamber, iris, and lens.

‖ Goldmann applanation tonometer taking three replicate measurements for each eye using the same calibrated tonometer at each visit.

¶ Complete blood count, differential, platelet count, cholesterol (total, HDL, and LDL), triglycerides, total protein, glucose, creatinine, urea nitrogen, bilirubin, alkaline phosphatase, SGOT, SGPT, sodium, potassium, calcium, and chloride.

** Including evaluation for albumin and sugar.

Demographics and Withdrawals

Of the 268 patients initially enrolled, 128 were assigned to the latanoprost group and 140 to the timolol group. No significant difference in age, sex, race, family history of glaucoma, number of eyes treated per patient, iris color, diagnosis or previous medical therapy existed between the two groups of patients (Tables 2 and 3). Ten patients from each group dropped out of the study for the reasons indicated in Table 4. Four patients receiving timolol and none receiving latanoprost were withdrawn from the study because of inadequate IOP control (Table 4).

Data Analysis

A two-tailed, paired or unpaired Student's t test was used as appropriate for statistical evaluation of differences between treatment and baseline values or between the latanoprost and timolol groups. Differences in diurnal IOP values between the latanoprost and timolol groups were determined using analysis of covariance with treatment groups and centers as factors and baseline IOPs as covariants. If both eyes of a patient were treated, a mean value of the two eyes was used for analysis. Protocol violations prevented inclusion of at least one IOP measurement from each of 24 patients treated with latanoprost and 26 treated with timolol. Overall, 11 patients had one measurement excluded, 28 had 2 excluded, 5 had 3 excluded, 1 had all except baseline measurements excluded (instilled study medication before the 8:00 AM IOP measurement on each visit), and 5 had all excluded (because of insufficient washout of previous β-blocker therapy). Thirty of these patients had the 12:00 noon and 4:00 PM measurements on their 6-month visit excluded because of failure to receive the 8:00 AM dose of the study medication on that day. When analyzed by including, rather than excluding, the IOPs during protocol violations, the significance of the findings did not change.

Results

Intraocular Pressure

Compared with baseline measurements, both latanoprost and timolol caused a significant ($P < 0.001$) reduction of IOP throughout the duration of therapy (Figs 1 and 2).

Table 2. Demographic Characteristics of Patients*

Characteristics	Timolol (n = 140)	Latanoprost (n = 128)
Age (yrs)		
Mean ± SD	63 ± 11	61 ± 12
Range	33-90	30-89
Sex		
M	56 (40)	58 (45)
F	84 (60)	70 (55)
Race		
White	91 (65)	94 (73)
Black	38 (27)	27 (21)
Hispanic	10 (7)	6 (5)
Asian	1 (1)	1 (1)
Family history of glaucoma or ocular hypertension	52 (37)	43 (34)

SD = standard deviation.

* Values in parentheses are percentages.

From 2 weeks to 6 months, the IOP remained stable in each treatment group (Fig 1). Latanoprost was a significantly ($P < 0.001$) more effective hypotensive agent compared with timolol (Figs 1 and 2). At 6 months, diurnal measurements (mean ± standard error) of IOP were reduced by 6.7 ± 3.4 mmHg (27%) with latanoprost and by 4.9 ± 2.9 mmHg (20%) with timolol compared with baseline measurements (Fig 2). None of the following factors significantly altered the effect of either latanoprost or timolol on IOP: sex, age, race, iris color, diagnosis (ocular hypertension versus glaucoma), or previous use of medical therapy (including β-blockers) for glaucoma.

Conjunctival Hyperemia

In general, mean conjunctival hyperemia was graded slightly higher in latanoprost-treated compared with timolol-treated eyes throughout the course of therapy. On a relative scale of 0 to 3, latanoprost-treated eyes were graded at 0.4 and timolol-treated eyes at 0.3 for hyperemia (Table 5).

Iris Color

A definite change in iris color was observed in both eyes of 1 of the 128 patients treated with latanoprost and none of the 140 patients treated with timolol. An additional three patients (both eyes of each) from the latanoprost group were suspects for these color changes. All four of these patients showed a concentric heterochromia on baseline photographs, with the stroma around the sphincter having a darker appearance than the peripheral iris stroma. Sixty of the 128 patients treated with latanoprost and 56 of the 140 treated with timolol showed this concentric heterochromia at baseline. Darkening of the peripheral iris stroma occurred or was suspected in these four patients, producing a more uniform iris color. The iris color change was suspected as early as 4.5 months after initiation of treatment. Nevi, or freckles of the iris, were not affected by latanoprost treatment.

Other Ocular Side Effects and Adverse Events

Serious ocular adverse events did not occur in any patient in either the latanoprost or timolol group. Otherwise, 20 ocular adverse events occurred in 10 (8%) of the 128 patients in the latanoprost group and 17 events in 16 (11%) of the 140 patients in the timolol group (Table 6). These ocular adverse effects included apparent worsening of the visual fields in one patient from each group.

Ocular signs and symptoms, excluding the adverse events, were reported at least once during the 6 months of treatment by 62 (48%) and 85 (61%) of the patients treated with latanoprost and timolol, respectively (Table 7). Stinging, itching, foreign body sensation, and tearing occurred more frequently in the timolol group, whereas blurred vision and dry eye were more common in the latanoprost group (Table 7).

With the exception of 4.5-month visit, at which time 28 (20%) patients treated with timolol and 17 (13%) treated with latanoprost reported ocular symptoms, no

Table 3. Baseline Characteristics of the Pairs of Eyes of Each Patient*

Characteristics	Timolol (n = 140)	Latanoprost (n = 128)
No. of eyes treated per patient		
One eye	20 (14)	21 (16)
Both eyes	120 (86)	107 (84)
Iris color		
Brown	71 (51)	68 (53)
Blue/green/gray	52 (37)	44 (34)
Hazel	17 (12)	16 (13)
Diagnosis		
Ocular hypertension	90 (64)	80 (63)
Primary open-angle glaucoma	45 (32)	39 (30)
Exfoliation	2 (1)	3 (2)
Pigmentary dispersion	1 (1)	3 (2)
Different diagnosis OD versus OS	2 (1)	3 (2)
No. of glaucoma medications per patient		
0	52 (37)	56 (44)
1	67 (48)	49 (38)
2	19 (14)	21 (16)
3	2 (1)	2 (2)
Glaucoma therapy		
β-adrenergic blocker	78 (56)	71 (55)
Adrenergic agonist	8 (6)	6 (5)
Cholinergic agonist	8 (6)	8 (6)
CAI	5 (4)	6 (5)
Other	7 (5)	1 (1)

OD = right eye; OS = left eye; CAI = carbonic anhydrase inhibitors.

* Values are no. (%).

Table 4. Numbers of and Reasons for Patient Withdrawals from Study

Treatment	Completions	Withdrawals*			
		Inadequate IOP Control	*Ocular Reasons*	*Systemic Medical Reasons*	*Nonmedical Reasons*
Latanoprost (n = 128)	118	0	2†	4§	4¶
Timolol (n = 140)	130	4	2‡	3‖	1**

IOP = intraocular pressure.

* Not necessarily related to treatment.

† Including allergic blepharoconjunctivitis.

‡ Including swelling of eyelids and allergic conjunctivitis.

§ Including palpitations, peptic ulcer symptoms, and maculopapular rash (two patients).

‖ Including palpitations, shortness of breath with subsequent bypass surgery, and status post mastectomy for breast cancer.

¶ Including left country for family emergency, lost to follow-up, moved out of state, and dropped out due to time constraints.

** Patient decided to withdraw from study without specifying a reason.

significant difference in ocular symptoms were reported between the two groups throughout the course of therapy.

Superficial punctate keratopathy (SPK) was reported in 17 (13%) patients treated with latanoprost and in 25 (18%) treated with timolol. In two of these patients from each group, SPK was found only at baseline before any study drug was applied. In two other patients treated with latanoprost, SPK was found at all visits, including baseline. In some patients, the SPK may have resulted from frequent tonometry and instillation of local anesthetic drugs.

Neither timolol nor latanoprost altered any of the following compared with baseline measurements: visual acuity, refraction, or slit-lamp biomicroscopic examination, including anterior chamber flare or cellular response.

Systemic Side Effects and Adverse Events

Serious adverse events occurred in 8 (6%) of the 128 patients treated with latanoprost, and in 10 (7%) of the 140 treated with timolol (Table 6). Of these patients with serious events, two may have been exacerbated by the treatment. Both patients were receiving timolol: one with shortness of breath, requiring discontinuation of the study drug, and the other with sick sinus syndrome with syncope (Table 6).

Excluding serious adverse events, 18 (14%) patients receiving latanoprost reported 20 additional nonocular adverse events, and 23 (16%) patients receiving timolol reported 33 events (Table 6). In addition to these adverse events, 34 (27%) of the patients treated with latanoprost reported 47 nonocular signs and symptoms, and 22 (16%)

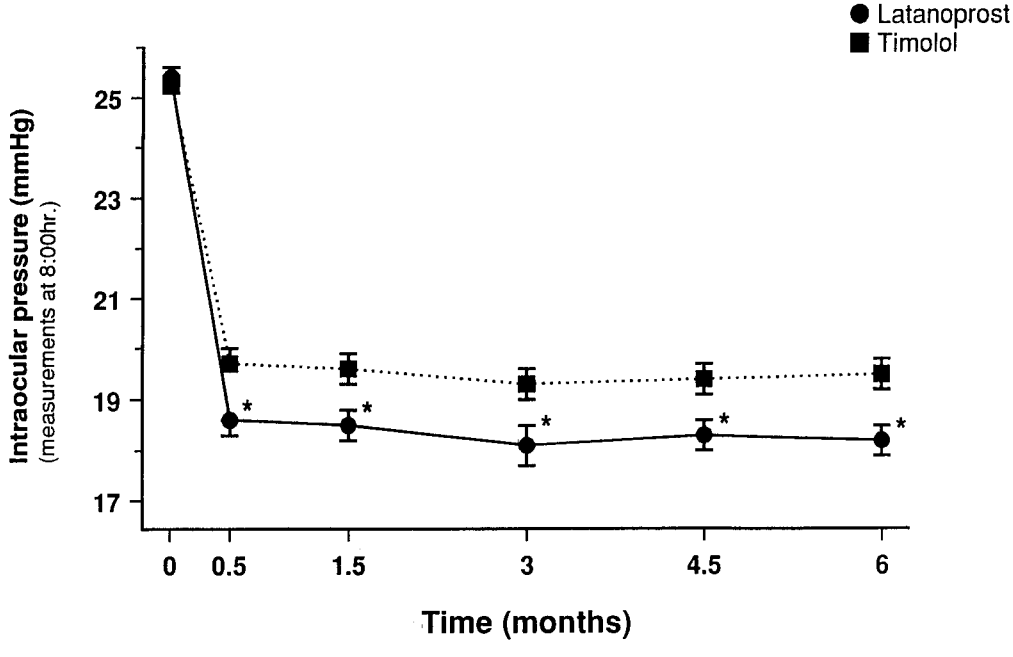

Figure 1. Effect of 0.005% latanoprost (n = 128) applied once daily (at 8:00 PM) and 0.5% timolol (n = 140) applied twice daily (at 8:00 AM and 8:00 PM) on intraocular pressure (IOP) as determined at 8:00 AM (12 hours after the last dose) in patients with ocular hypertension or glaucoma. The IOP of patients with protocol violations were not included (see the Patients and Methods section). If both eyes of a patient were treated, a mean value of both eyes was used. Each value represents a mean ± standard error of the mean. All values were significantly ($P < 0.001$) reduced compared with baseline measurements. Asterisks = a significant ($P < 0.001$) further reduction of IOP produced by latanoprost compared with timolol.

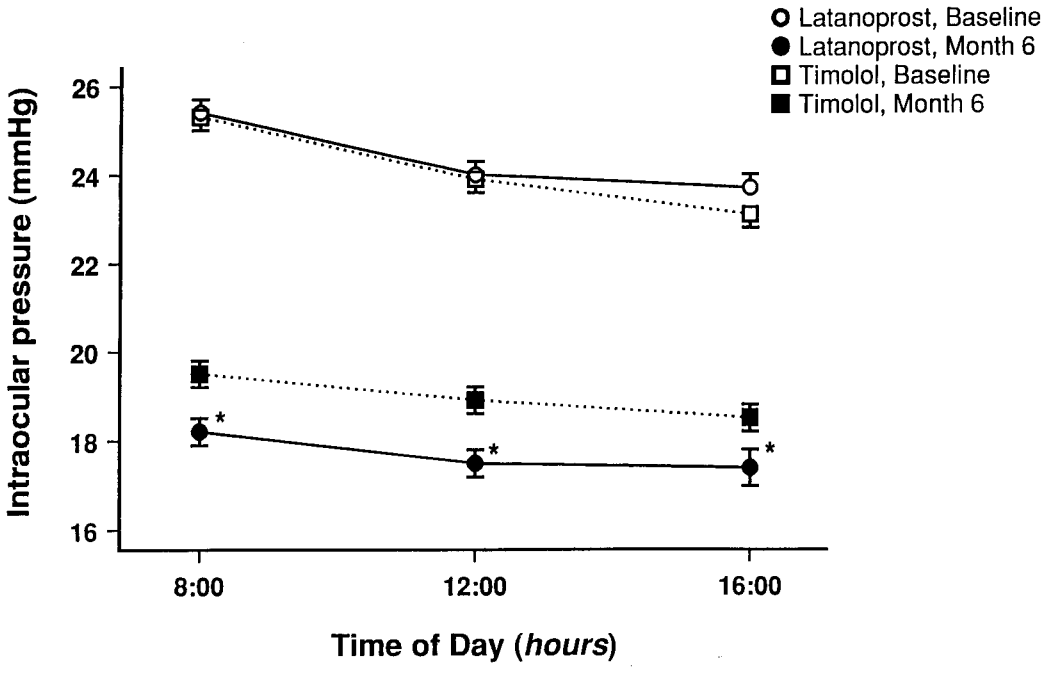

Figure 2. Diurnal effect of latanoprost and timolol on IOP as determined on baseline day and after 6 months of treatment. Also see legend of Figure 1.

of those treated with timolol reported 35 nonocular signs and symptoms.

Heart rate did not change significantly in the latanoprost group. However, in the timolol group, heart rate (mean ± SD) was significantly ($P < 0.001$) reduced from 75 ± 10 to 71 ± 10 beats per minute at 6 months (Table 8). Neither blood pressure (Table 8) nor laboratory values (blood or urine) changed significantly in either group.

Discussion

The results of this study show that 0.005% latanoprost applied topically once daily is a more effective ocular hypotensive agent than 0.5% timolol applied twice daily. The concentration of latanoprost is 1/100 that of timolol; therefore, latanoprost is at least 100-fold more potent than timolol. The hypotensive effect is maintained, without any evidence of drift, from 2 weeks to 6 months of treatment. More subjective ocular side effects occur with timolol compared with latanoprost. Intraocular inflammatory effects do not occur. Although blood pressure is not altered in either group, heart rate is significantly reduced by timolol, but not by latanoprost. Although latanoprost produces slightly more conjunctival hyperemia than timolol, this mild side effect is well tolerated and virtually unnoticed by the patients.

The study design includes IOP measurements at 4, 8, and 12 hours after the last dose of timolol, and 12, 16, and 20 hours after the last dose of latanoprost. At each time point, latanoprost was more effective than timolol. Both drugs provide approximately 24 hours of IOP control with minimal diurnal fluctuation. Unlike other drugs with a shorter duration of action, such as pilocarpine, dorzolamide, or apraclonidine, there is no appreciable peak or trough effect after each dose of timolol or latanoprost. Therefore, the greater efficacy of latanoprost compared with timolol is unlikely due to differences in the timing of the IOP measurements.

Of the PG analogues reported in clinical trials, latanoprost appears to provide the best separation between ocular hypotensive efficacy and side effects. $PGF_{2\alpha}$ tromethamine salt,[27,28] $PGF_{2\alpha}$-1-isopropyl ester,[4–6] 15-propionate-$PGF_{2\alpha}$-1-isopropyl ester (diester),[7] PGD_2,[9] BW245C,[9] PGE_2 analogue,[3] and UF-021[10] either do not effectively reduce IOP or produce unacceptable side effects. Of these analogues, PGD_2,[9] BW245C,[9] and the PGE_2 analogue[3] were found to cause an initial mean rise in IOP of as much as 4 mmHg during the first 2 hours after administration. Although IOP was not measured during the first few hours after latanoprost administration in the current study, other publications demonstrate that the 17-phenyl-substituted $PGF_{2\alpha}$ analogues (latanoprost or its epimeric mixture PhXA34) do not raise IOP at any time after administration.[8,11,12,15–21] Although many of the subjective side effects and conjunctival hyperemia were assessed 12 to 20 hours after the last latanoprost dose in the current study, previous studies indicate that side effects are no different in the first, compared with second, 12 hours after administration of PhXA34 or latanoprost.[8,11,16,17,21] Evening, rather than morning, administration of latanoprost was chosen to potentially block an early morning diurnal spike of IOP, not to reduce side effects. The time course and the magnitude of the conjunctival hyperemia after PhXA34[8,11] or latanoprost[16,17,21] are distinctly different from that occurring after other PG analogues.[1–7,9,27,28] The peak hyperemia occurs earlier, usually within the first hour, and is much greater in magnitude with the latter analogues.

Table 5. Relative Conjunctival Hyperemia at Baseline and during the Course of Treatment*

Treatment Group	Baseline		2 Wks	1.5 Mos	3 Mos	4.5 Mos	6 Mos	
	8 AM	12 Noon	4 PM	8 AM	8 AM	8 AM	8 AM	12 Noon	4 PM
Timolol	0.3 ± 0.4	0.3 ± 0.3	0.3 ± 0.4	0.3 ± 0.3	0.3 ± 0.4	0.4 ± 0.4	0.3 ± 0.3	0.3 ± 0.3	0.3 ± 0.3
Latanoprost	0.2 ± 0.4	0.3 ± 0.4	0.3 ± 0.4	0.5 ± 0.5	0.4 ± 0.5	0.5 ± 0.4	0.4 ± 0.4	0.4 ± 0.4	0.4 ± 0.4

*Mean ± standard deviation in relative units (graded on a scale of 0–3; see footnote to Table 1 for details); n = 118–140 for each value.

Latanoprost did not produce significant aqueous flare or an anterior chamber cellular response, similar to the results in all clinical studies previously reported with latanoprost or any other PG analogue.[1–12,14,16–25,27–30] Using very sensitive techniques to assess the blood–aqueous barrier after latanoprost treatment in 40 subjects, polarization of cameral fluorescence, intensity of back-scattered light from the anterior chamber, or cameral fluorescence after oral fluorescein did not demonstrate any significant effect on blood–aqueous barrier permeability.[19] In addition, a laser flare-cell meter failed to demonstrate a breakdown of the blood–aqueous barrier after latanoprost treatment (Hotehama and Mishima, unpublished data; presented at the 1992 ARVO Annual Meeting). On the other hand, many studies in experimental animals, es-

Table 6. Number of Patients with Adverse Events (not necessarily related to treatment)

Adverse Events	Timolol (n = 140)	Latanoprost (n = 128)
Serious*	10†	8‡
Not serious§		
Ocular	16‖	10¶
Nonocular	23**	18††

*Defined as potentially fatal, life-threatening, permanently disabling, requiring hospitalization, cancer, or a drug overdose.

† Includes squamous cell carcinoma in skin of hand; shoulder surgery; chest pain; surgery for cholelithiasis; shortness of breath with subsequent bypass surgery (withdrew from study, possibly treatment related); syncope with sick sinus syndrome (possibly treatment related); *Escherichia coli* septicemia with fatigue; hysterectomy for vaginal spotting; cerebrovascular accident due to seizure; mastectomy for breast cancer (withdrew from study).

‡ Includes suspected myocardial infarction; cholelithiasis; liver biopsy for pre-existing abnormal liver function tests; renal stones; neck surgery; gynecomastia; peptic ulcer; exacerbation of manic phase.

§ Seven patients had both ocular and nonocular adverse events; 14 patients had more than one adverse event.

‖ Includes conjunctivitis (allergic or infectious), pain, conjunctival hyperemia, photophobia, chalazion, eyelid edema, subconjunctival hemorrhage, posterior vitreous detachment, visual field defect, blepharitis, ptosis, hordeolum, foreign body sensation.

¶ Includes increased iridial pigmentation, blurred vision, conjunctival chemosis, burning, epiphora, conjunctival hyperemia, eyelid edema, ocular migraine, dipolpia with VIth nerve palsy, hordeolum, ecchymosis of eyelid, posterior vitreous detachment, constriction of visual fields, pain, blepharitis.

** Includes bronchial infection, infected cyst on leg, palpitations, weakness, anxiety, dizziness, coryza, flu, breakthrough menstrual bleeding, low serum potassium level, eczema, gastric ulcer, urinary tract infection, abnormal liver function tests, increased triglyceride levels, dyspnea, gastric pain, root canal surgery, ear infection, headache, cholecystitis, memory loss, eosinophilia, redness and swelling of nipples, upper respiratory tract infection, rhinorrhea.

†† Includes mole removal from neck with infected wound, sinus infection, uterine cervical infection, palpitations, progression of preexisting anemia, sinus infection, bronchitis, abdominal lump, bunion surgery, bursitis in shoulder, urinary tract infection, infected cyst on neck, hematuria, itchiness of arms and abdomen, coryza, generalized maculopapular rash, upper respiratory tract infection.

Table 7. Number of Patients with the Specified Symptom or Sign at Least Once during the 6 Months of Therapy (not necessarily related to treatment), Excluding Adverse Events*

Symptom/Sign	Timolol (n = 140)	Latanoprost (n = 128)
Burning	18 (13)	13 (10)
Stinging	17 (12)	8 (6)
Blurred vision	9 (6)	13 (10)
Itching	15 (11)	7 (5)
Foreign body sensation	16 (11)	5 (4)
Tearing	13 (9)	3 (2)
Dry eye	6 (4)	10 (8)
Eye pain	6 (4)	2 (2)
Eyelid pain or discomfort	4 (3)	9 (7)
Conjunctival hyperemia/hemorrhage	3 (2)	7 (5)
Photophobia	5 (4)	4 (3)
Other†	17 (12)	22 (17)
Total	85 (61)	62 (48)

* Values in parentheses are percentages.

† Includes eye irritation, floaters, photopsia, eyelid edema, discharge, eyelid twitch, tiredness of eyes, visual disturbance or variability, diplopia, conjunctivitis, ptosis, feeling of fullness.

pecially when using very high doses of certain PGs in rabbits, have demonstrated a pronounced breakdown of the blood–aqueous barrier.[1]

Latanoprost offers several potential advantages over currently available medications for glaucoma therapy. Unlike β-blockers, carbonic anhydrase inhibitors, and α_2-agonists, it acts on outflow rather than formation of aqueous humor.[15,31] Virtually all glaucomas result from impaired outflow, but not from excessive formation of aqueous humor. Avascular ocular structures depend on aqueous flow for metabolic exchanges; therefore, chronic excessive reduction of aqueous humor formation may have deleterious effects.[32] Unlike β-adrenergic blockers, which do not further reduce aqueous flow at night beyond the decrease already achieved during sleep,[33] latanoprost reduces IOP equally as well at night as during the day (Bito et al, unpublished data; presented at the 1994 ARVO Annual Meeting). This represents a potential advantage because glaucomatous damage may occur during sleep when ocular perfusion pressure may be reduced because of low systemic blood pressure.[34] Furthermore, because latanoprost increases uveoscleral outflow,[15] it can theoretically reduce IOP below episcleral venous pressure, unlike drugs that act by either reducing aqueous humor production or increasing outflow facility. This may be advantageous in patients with normal-tension glaucoma in whom progressive loss at night may develop and who may require very low IOPs.

Another important consideration is that nonselective β-adrenergic blockers are known to cause cardiovascular, pulmonary, and other systemic side effects in some patients. Although additional studies are required, latanoprost did not produce systemic side effects in the current or previously reported studies, and is not expected to do so based on pharmacokinetic considerations (Sjoquist et al, unpublished data; presented at the 1994 ARVO Annual Meeting).[25] However, in patients requiring combined therapy for adequate control of IOP, the ocular hypotensive effects of latanoprost and other PG analogues and prodrugs are additive with those of aqueous humor suppressants (Alm et al, unpublished data; presented at the 1993 ARVO Annual Meeting; Rulo et al, unpublished data; presented at the 1993 ARVO Annual Meeting).[29,30]

Long-term treatment with high doses of PGs caused increased pigmentation of the iris in cynomologus monkeys (unpublished data, Pharmacia Pharmaceuticals). Histopathologic studies of these irides show increased melanogenesis without proliferation of melanocytes. Because of this finding, magnified color photographs were taken at baseline and at 1.5- to 3-month intervals during treatment in the current study. Careful review of these photographs showed 1 definite and 3 possible cases of increased iris pigmentation of the 128 patients treated with latanoprost. In all four patients, the baseline photographs showed a characteristic pattern of a brown or light-brown central portion around the sphincter, fading to a much lighter bluish or greenish periphery. However,

Table 8. Resting Brachial Blood Pressure and Heart Rate at Baseline and during the Course of Treatment*

	Timolol			Latanoprost		
	SBP (mmHg)	*DBP (mmHg)*	*HR (beats/min)*	*SBP (mmHg)*	*DBP (mmHg)*	*HR (beats/min)*
Baseline	139 ± 19	82 ± 10	75 ± 10	137 ± 18	82 ± 10	75 ± 11
2 wks	137 ± 18	82 ± 10	73 ± 9†	136 ± 16	82 ± 11	74 ± 10
3 mos	136 ± 19†	82 ± 10	71 ± 10†	137 ± 17	82 ± 10	73 ± 10
6 mos	136 ± 19	82 ± 12	71 ± 10†	137 ± 18	82 ± 11	74 ± 10

SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate.

* Values represent mean ± standard deviation; n = 117–140 for each measurement.

† $P < 0.05$ compared with baseline measurements using an unpaired, two-tailed Student's *t* test.

not all such concentrically heterochromic eyes showed a change in pigmentation.

The mechanism of this unusual finding currently is under extensive investigation. It does not appear to be due to proliferation of melanocytes, but rather to stimulation of melanin synthesis (melanogenesis) in the iridial melanocytes (unpublished data, Pharmacia Pharmaceuticals). Prostaglandins are known to be involved with the responses of epidermal melanocytes to ultraviolet light in the tanning reaction in the skin.[35] However, in the current study, there was no indication of increased pigmentation of the periorbital skin, which likely was exposed to the topically applied drug. Therefore, the increased pigmentation in the iris must involve a process that is unique to iridial melanocytes. Furthermore, the finding that this change in pigmentation occurs only in irides showing a baseline, characteristic, concentric heterochromia suggests that only irides with certain physiologic characteristics are susceptible.

The only patient of the 128 treated with latanoprost showing a definite latanoprost-induced change in iris color reported a history of having darker-colored eyes during his youth. Over the last several years, he described loss of the brown color. Although speculative, the latanoprost treatment apparently restored iris pigmentation that formerly was lost. The apparent increase in melanogenesis in this patient seemed to require maintenance of the latanoprost treatment. Upon discontinuation of treatment, the pigmentation did not progress. In fact, the latanoprost-induced pigmentation may be regressing in this patient, although longer follow-up is required to establish definite reversibility.

In conclusion, latanoprost has several advantages over β-blockers, including its potency, efficacy during the day and night, mechanism of action on outflow, additivity with aqueous humor suppressants, and probable safer systemic side effect profile. Although the unusual side effect of increased iris pigmentation must be evaluated further, the results of this study suggest that latanoprost will be a useful initial treatment for glaucoma.

Appendix

Members of the United States Latanoprost Study Group:

Devers Eye Institute (Portland, Oregon): Principal Investigator: G. A. Cioffi, MD; Co-investigator: E. M. Van Buskirk, MD; Study Coordinator: J. Fraser, COT; *Medical University of South Carolina (Charleston, South Carolina):* Principal Investigator: W. C. Stewart, MD; Study Coordinator: J. A. Stewart, RN; *Mt. Sinai Medical Center (New York, New York):* Principal Investigators: J. Lustgarten, MD (center in River Edge, NJ), R. A. Schumer, MD, PhD; Co-investigator: S. M. Podos, MD; Study Coordinators: M. Arroyo, S. Nitzberg; *New York Eye and Ear Infirmary (New York, New York):* Principal Investigator: R. Ritch, MD; Co-investigators: G. Abundo, MD, R. Caronia, MD, J. Liebmann, MD, D. Steinberger, MD; *Northwestern University (Chicago, Illinois):* Principal Investigator: T. Krupin, MD; Co-investigators: L. F. Rosenberg, MD, J. M. Ruderman, MD; Study Coordinator: K. Clarkson; *University of California, San Diego (La Jolla, California):* Principal Investigator: R. N. Weinreb, MD; Study Coordinator: R. Ochabsi, MD; *University of Florida (Gainesville, Florida):* Principal Investigator: M. Sherwood, MD; Co-investigators: M. F. Smith, MD, D. W. Stokes, MD; Study Coordinator: Z. S. Zam; *University of Illinois (Chicago, Illinois):* Principal Investigator: J. Wilensky, MD; Co-investigators: D. Hillman, MD, B. Kaplan, MD; Study Coordinators: V. Gates, COT, C. Nail, COMT; *University of Louisville (Louisville, Kentucky):* Principal Investigator: T. Zimmerman, MD, PhD; Co-investigators: R. Fechtner, MD, R. Fenton, MD; Study Coordinator: J. Fenton; *University of Michigan (Ann Arbor, Michigan):* Principal Investigator: E. J. Higginbotham, MD (now affiliated with the University of Maryland, Baltimore, MD); Co-investigator: A. T. Johnson, MD, PhD; Study Coordinator: C. J. Pollack-Rundle; *University of Nebraska Medical Center (Omaha, Nebraska):* Principal Investigator: C. B. Camras, MD; Co-investigators: E. Weiss, OD, M. E. Yablonski, MD, PhD, M. H. Tannenbaum, MD, F. Ibrahim, MD, E. Ohia, MD; Study Coordinator: D. Neely, COMT; *University of Southern California (Los Angeles, California):* Principal Investigator: D. Minckler, MD; Co-investigators: D. Heuer, MD, P. Lee, MD; Study Coordinator: M. Padea; *University of Wisconsin (Madison, Wisconsin):* Principal Investigator: P. L. Kaufman, MD; Co-investigator: G. A. Heatley, MD; Study Coordinator: M. A. Vanderhof-Young; *Washington University School of Medicine (St. Louis, Missouri):* Principal Investigator: M. Wax, MD; Study Coordinator: A. Jones; *Wills Eye Hospital (Philadelphia, Pennsylvania):* Principal Investigator: L. J. Katz, MD; Co-investigator: M. Moster, MD; Study Coordinator: B. Parker; *Wilmer Eye Institute at Johns Hopkins University (Baltimore, Maryland):* Principal Investigator: A. L. Robin, MD; Co-investigator: M. Juzych, MD; Study Coordinator: M. Brummett; *Sponsor:* Pharmacia Pharmaceuticals (Uppsala, Sweden): *Study Director:* U. Parkhede.

References

1. Camras CB. Prostaglandins. In: Ritch R, Shields MB, Krupin T, eds. The Glaucomas, 2nd ed. St. Louis: Mosby-Year Book, chapter 69 1995;1449–61.
2. Alm A. The potential of prostaglandin derivatives in glaucoma therapy. Curr Opin Ophthalmol 1993;4(2):44–50.
3. Flach AJ, Eliason JA. Topical prostaglandin E_2 effects on normal human intraocular pressure. J Ocul Pharmacol 1988;4:13–18. Erratum: J Ocul Pharmacol 1991;7:189.
4. Camras CB, Siebold EC, Lustgarten JS, et al. Maintained reduction of intraocular pressure by prostaglandin $F_{2\alpha}$-1-isopropyl ester applied in multiple doses in ocular hypertensive and glaucoma patients. Ophthalmology 1989;96: 1329–37.
5. Villumsen J, Alm A. Prostaglandin $F_{2\alpha}$-isopropylester eye drops: effects in normal human eyes. Br J Ophthalmol 1989;73:419–26.

6. Villumsen J, Alm A, Söderström M. Prostaglandin $F_{2\alpha}$- isopropylester eye drops: effect on intraocular pressure in open-angle glaucoma. Br J Ophthalmol 1989;73:975–9.
7. Villumsen J, Alm A. Ocular effects of two different prostaglandin $F_{2\alpha}$ esters. A doublemasked cross-over study on normotensive eyes. Acta Ophthalmol 1990;68:341–3.
8. Alm A, Villumsen J. PhXA34, a new potent ocular hypotensive drug. A study on dose-response relationship and on aqueous humor dynamics in healthy volunteers. Arch Ophthalmol 1991;109:1564–8.
9. Nakajima M, Goh Y, Azuma I, Hayaishi O. Effects of prostaglandin D_2 and its analogue, BW245C, on intraocular pressure in humans. Graefes Arch Clin Exp Ophthalmol 1991;229:411–3.
10. Sakurai M, Araie M, Oshika T, et al. Effects of topical application of UF-021, a novel prostaglandin derivative, on aqueous humor dynamics in normal human eyes. Jpn J Ophthalmol 1991;35:156–65.
11. Camras CB, Schumer RA, Marsk A, et al. Intraocular pressure reduction with PhXA34, a new prostaglandin analogue, in patients with ocular hypertension. Arch Ophthalmol 1992;110:1733–8.
12. Villumsen J, Alm A. PhXA34—a prostaglandin $F_{2\alpha}$ analogue. Effect on intraocular pressure in patients with ocular hypertension. Br J Ophthalmol 1992;76:214–7.
13. Tetsuka H, Tsuchisaka H, Kin K, et al. A mechanism for reducing intraocular pressure in normal volunteers using UF-021, a prostaglandin-related compound [in Japanese]. Nippon Ganka Gakkai Zasshi 1992;96:496–500.
14. Takase M, Murao M, Koyano S, et al. Ocular effects of topical instillation of UF-021 ophthalmic solution in healthy volunteers [in Japanese]. Nippon Ganka Gakkai Zasshi 1992;96:1261–7.
15. Toris CB, Camras CB, Yablonski ME. Effects of PhXA41, a new prostaglandin $F_{2\alpha}$ analog, on aqueous humor dynamics in human eyes. Ophthalmology 1993;100:1297–304.
16. Alm A, Villumsen J, Törnquist P, et al. Intraocular pressure-reducing effects of PhXA41 in patients with increased eye pressure. A one-month study. Ophthalmology 1993;100:1312–7.
17. Nagasubramanian S, Sheth GP, Hitchings RA, Stjernschantz J. Intraocular pressure-reducing effect of PhXA41 in ocular hypertension. Comparison of dose regimens. Ophthalmology 1993;100:1305–11.
18. Racz P, Ruzsonyi MR, Nagy ZT, Bito LZ. Maintained intraocular pressure reduction with once-a-day application of a new prostaglandin $F_{2\alpha}$ analogue (PhXA41). An in-hospital, placebo-controlled study. Arch Ophthalmol 1993;111:657–61.
19. Ziai N, Dolan JW, Kacere RD, Brubaker RF. The effects on aqueous dynamics of PhXA41, a new prostaglandin $F_{2\alpha}$ analogue, after topical application in normal and ocular hypertensive human eyes. Arch Ophthalmol 1993;111:1351–8.
20. Hotehama Y, Mishima H. Clinical efficacy of PhXA34 and PhXA41, two novel prostaglandin $F_{2\alpha}$-isopropyl ester analogues for glaucoma treatment. Jpn J Ophthalmol 1993;37:259–69.
21. Hotehama Y, Mishima HK, Kitazawa Y, Masuda K. Ocular hypotensive effect of PhXA41 in patients with ocular hypertension or primary open-angle glaucoma. Jpn J Ophthalmol 1993;37:270–4.
22. Azuma I. Clinical evaluation of UF-021 ophthalmic solution in glaucoma patients refractory to maximum tolerable therapy [in Japanese]. Nippon Ganka Gakkai Zasshi 1993;97:232–8.
23. Fujimori C, Yamabayashi S, Hosoda M, et al. The clinical evaluation of UF-021, a new prostaglandin related compound, in low tension glaucoma patients [in Japanese]. Nippon Ganka Gakkai Zasshi 1993;97:1231–5.
24. Stjernschantz J, Resul B. Phenyl substituted prostaglandin analogs for glaucoma treatment. Drugs Future 1992;17:691–704.
25. Bito LZ, Stjernschantz J, Resul B, et al. The ocular effects of prostaglandins and the therapeutic potential of a new $PGF_{2\alpha}$ analog, PhXA41 (latanoprost), for glaucoma management. J Lipid Mediat 1993;6:535–43.
26. Resul B, Stjernschantz J, No K, et al. Phenyl-substituted prostaglandins: potent and selective antiglaucoma agents. J Med Chem 1993;36:243–8.
27. Giuffrè G. The effects of prostaglandin $F_{2\alpha}$ in the human eye. Graefes Arch Clin Exp Ophthalmol 1985;222:139–41.
28. Lee P-Y, Shao H, Xu L, Qu C-K. The effect of prostaglandin $F_{2\alpha}$ on intraocular pressure in normotensive human subjects. Invest Ophthalmol Vis Sci 1988;29:1474–7.
29. Villumsen J, Alm A. The effect of adding prostaglandin $F_{2\alpha}$-isopropylester to timolol in patients with open angle glaucoma. Arch Ophthalmol 1990;108:1102–5.
30. Lee P-Y, Shao H, Camras CB, Podos SM. Additivity of prostaglandin $F_{2\alpha}$-1-isopropyl ester to timolol in glaucoma patients. Ophthalmology 1991;98:1079–82.
31. Camras CB. Mechanism of the prostaglandin-induced reduction of intraocular pressure in humans. In: Samuelsson B, Paoletti R, Ramwell PW, Vane JR, eds. Adv Prostaglandin Thromboxane Leukot Res, Vol 23. New York: Raven Press, 1995:519–25.
32. Bito LZ. Glaucoma: a physiologic perspective with Darwinian overtones. J Glaucoma 1992;1:193–205.
33. Topper JE, Brubaker RF. Effects of timolol, epinephrine, and acetazolamide on aqueous flow during sleep. Invest Ophthalmol Vis Sci 1985;26:1315–9.
34. Hayreh SS, Zimmerman MB, Podhajsky P, Alward WLM. Nocturnal arterial hypotension and its role in optic nerve head and ocular ischemic disorders. Am J Ophthalmol 1994;117:603–24.
35. Nordlund JJ, Abdel-Malek ZA, Boissy RE, Rheins LA. Pigment cell biology: an historical review. J Invest Dermatol 1989;92(Suppl 4):53S–60S.