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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 Four patients treated with timolol and none treated with latanoprost were withdrawn from the study because of inadequate IOP control.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*

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

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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-

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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).

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