A Double-masked, Randomized Clinical Trial Comparing Latanoprost with Unoprostone in Patients with Open-angle Glaucoma or Ocular Hypertension

Remo Susanna, Jr., MD, Jair Giampani, Jr., MD, Adriana S. Borges, MD, Roberto M. Vessani, MD, Marcelo L.S. Jordao, MD

Purpose: To compare the intraocular pressure (IOP) reducing effect and safety of latanoprost 0.005% once daily with unoprostone 0.12% twice daily in patients with primary open-angle glaucoma (POAG) or ocular hypertension (OH).

Design: An 8-week, double-masked, randomized, parallel-group, single-center clinical trial.

Participants: A total of 108 patients with POAG or OH were enrolled.

Interventions: After completing a wash-out of ocular hypotensive medications, patients were randomized to receive either latanoprost once daily in the evening plus placebo once daily in the morning, or unoprostone twice daily (morning and evening).

Main Outcome Measures: IOP was measured at 10:00 AM and at 5:00 PM at baseline and at week 8, and before 12:00 noon at week 2. Ocular and systemic safety assessments were performed.

Results: From an overall baseline of 24.1 mmHg, latanoprost reduced IOP by 6.7 mmHg (28%) and unoprostone reduced IOP by 3.3 mmHg (14%). The difference between the groups of 3.4 mmHg was significant ($P < 0.001$, analysis of covariance; 95% confidence interval [CI]: −4.7 to −2.1) in favor of latanoprost. A ≥30% reduction in mean IOP from baseline was achieved by 44% of latanoprost-treated patients compared with 8% of unoprostone-treated patients. The incidence of adverse events was low and comparable between the groups.

Conclusions: Latanoprost administered once daily was significantly more effective in reducing IOP compared with unoprostone administered twice daily in patients with POAG and OH. *Ophthalmology 2001;108: 259–263 © 2001 by the American Academy of Ophthalmology.*

Latanoprost is a prostaglandin $F_{2\alpha}$ analog and a selective F-prostaglandin (FP) receptor agonist that effectively reduces intraocular pressure (IOP) in patients with glaucoma and ocular hypertension.[1–4] Both preclinical and clinical data demonstrate that the mechanism of action is increased aqueous humor outflow by means of the uveoscleral route.[5–7] The optimal dosage of latanoprost 0.005% has been shown to be one drop once daily.[8] In phase III clinical trials, the IOP-reducing effect of latanoprost was shown to be better than timolol[1,3,4] or equal to timolol.[2]

Isopropyl unoprostone, an analog of a prostaglandin metabolite and formerly known as UF–021, has been available since 1994 in Japan.[9] Unoprostone acts on the uveoscleral outflow.[10] Unoprostone is administered in the concentration of 0.12% twice daily at a 12-h interval. In a phase III clinical trial, the IOP-reducing effect of unoprostone was found to be equal to that of timolol.[11]

To the best of our knowledge, there are no published clinical studies comparing latanoprost and unoprostone. In a recent review on prostaglandin analogs,[12] the need for a direct comparative clinical study between latanoprost and unoprostone was highlighted. The purpose of our study was to compare the IOP-reducing effect and safety of latanoprost 0.005% administered once daily in the evening with unoprostone 0.12% administered twice daily during 8 weeks of treatment.

Patients and Methods

This parallel-group, double-masked, randomized clinical trial was conducted at the Glaucoma Service, Department of Ophthalmology and Otolaringology, University of São Paulo, Brazil. The study was performed according to the principles of the Declaration of Helsinki and approved by the local ethics committee. All patients signed an informed consent form after receiving detailed information about the study.

Patients at least 18 years of age, with currently untreated unilateral or bilateral primary open-angle glaucoma and an IOP ≥21 mmHg or ocular hypertension and an IOP ≥25 mmHg or

Originally received: February 25, 2000.
Accepted: August 28, 2000. Manuscript no. 200109.

Glaucoma Service, Department of Ophthalmology and Otolaringology, Faculty of Medicine, University of São Paulo, São Paulo, Brazil.

Supported by Pharmacia & Upjohn, Uppsala, Sweden.

Reprint requests to: Remo Susanna, Jr., MD, Glaucoma Service, Department of Ophthalmology and Otolaringology, University of São Paulo, São Paulo, Brazil. E-mail: rsusanna@originet.com.br

ISSN 0161-6420/00/$–see front matter
PII S0161-6420(00)00495-4

greater were eligible for inclusion. Patients on ocular hypotensive treatment were also eligible provided they underwent an appropriate wash-out period before the baseline visit, according to the following schedule: 4 weeks for β-adrenergic antagonists, 2 weeks for adrenergic agonists, 5 days for cholinergic agonists and oral or topical carbonic anhydrase inhibitors. After wash-out, patients with an IOP 21 mmHg or greater in the morning at the baseline visit were eligible for inclusion.

The following ocular conditions were reason for exclusion: previous treatment with unoprostone or latanoprost, history of acute angle closure, current use of contact lenses, history of argon laser trabeculoplasty or ocular filtering surgical intervention, ocular surgery or inflammation/infection within 3 months before prestudy visit, hypersensitivity to benzalkonium chloride or to any other component in unoprostone or latanoprost eye drop solutions or other abnormal ocular condition or symptoms preventing the patient from entering the study. Women who were pregnant or breast-feeding, or of childbearing age and not using adequate contraceptive methods, were also excluded. Patients were also ineligible if they had participated in any other clinical trial within 1 month before the prestudy visit.

Eligible patients were randomized at the baseline visit to 8 weeks of treatment with either latanoprost once daily in the evening (10:00 PM) and placebo (vehicle) once daily in the morning (8:00 AM) or unoprostone twice daily (8:00 AM and 10:00 PM). Patients were dispensed study medication that was packaged in identical bottles according to a computer-generated randomization list provided by Pharmacia & Upjohn, Sweden. Disclosure envelopes were kept in a locked cabinet at the study site. In the event of an emergency requiring identification of the masked treatment, the envelope could be opened. No envelopes were opened during the trial.

The first study eye drops were instilled in the evening at baseline visit. The last drop of unoprostone was instilled at 8:00 AM of the week 8 visit, at least 2 hours before morning IOP measurements. The last drop of latanoprost was instilled at 10:00 PM the day before the week 8 visit.

Patients requiring bilateral IOP-reducing therapy were treated in both eyes, but only the eye(s) that fulfilled all inclusion criteria were designated as "study eyes." An eye not meeting all inclusion criteria could also be treated with the study drug provided that none of the exclusion criteria were met. In such cases, the allocated masked drug as for the study eye was used. The eye was not included in the efficacy analysis but was included in the safety analysis.

Concomitant medications were recorded throughout the study period. Systemic medication known to affect IOP (e.g., β-adrenergic antagonists, adrenergic agonists, calcium channel blockers, ACE inhibitors and/or angiotensin II receptor blockers) was not to be initiated or altered during the study.

The schedule of examinations and procedures is presented in Table 1. Study visits took place at prestudy, baseline, week 2, and week 8. At all study visits, best-corrected visual acuity was determined, the lids were examined, and slit-lamp examination of the conjunctiva, cornea, anterior chamber, iris, and lens was performed. At prestudy and week 8, ophthalmoscopy with dilated pupils was performed after IOP measurements. For all examinations, any abnormal findings were recorded. If a visual field had been obtained within approximately 1 year before study start, no additional test was required at the prestudy visit; otherwise a visual field examination (Humphrey Field Analyzer program 24:2) was to be performed.

The IOP was measured with a Goldmann applanation tonometer. Three measurements were performed in each eye. The mean of the three values was used in the statistical analysis. IOP measurements were performed at 10:00 AM and 5:00 PM at baseline visit and at the week 8 visit, and before 12:00 noon at the week 2 visit. At least 2 hours should have elapsed from the time the drug was administered to the morning IOP measurement. The mean IOP reduction was defined as the mean of 10:00 AM and 5:00 PM IOP measurements.

Table 1. Schedule of Examinations and Procedures

Examinations	Prestudy	Baseline	Week 2	Week 8	Follow-up
Medical and ocular history	X*				
Visual acuity	X	X	X	X	
Lid and slit-lamp examination	X	X	X	X	
Ophthalmoscopy	X			X	
Intraocular pressure†	X	XX	X	XX	
Adverse events			X	X	X

*If a visual field had been obtained within approximately 1 year before study start, no additional test was required at the prestudy visit.

†At baseline and 8 weeks, IOP was determined two times during the day, at 10:00 AM and 5:00 PM.

Adverse events, defined as any untoward medical occurrence in a patient enrolled in the study (whether or not a causal relationship with the treatment was suspected), were included in the safety assessment. Serious adverse events, defined as death, life-threatening conditions, hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, were to be reported in an expedited manner.

Statistical Analysis

The sample size of 108 patients (54 per treatment group) was calculated based on the assumption that there is a true difference between treatments of 2.0 mmHg and a standard deviation (SD) of 3.5 mmHg, at a significance level of 0.05 and power of 80%, and allowing for 10% withdrawals.

An analysis of covariance (ANCOVA) with mean IOP change from baseline to week 8 for the study eye(s) as response variable, treatment group as factor, and baseline mean IOP as a covariate was performed. A 95% confidence interval based on the least square estimate for the difference in the mean IOP change between the two treatment groups (latanoprost minus unoprostone) was constructed. If both eyes of a patient were eligible as study eyes, a mean value of the two eyes was used for the efficacy analysis.

Two approaches to the analysis were used: all treated patients with last observation carried forward (intention-to-treat, ITT) and per-protocol (PP) analysis. In the ITT analysis, all randomized patients who received at least one drop of study medication were included. For withdrawn patients, efficacy data from the last available visit were used. In the PP analysis, patients who did not complete the study as well as patients with major protocol violations were excluded. These decisions were made before breaking the masking/code. The two approaches gave similar results and, therefore, data from the ITT population are presented.

Results

A total of 108 patients were included in the study, 54 in the latanoprost group and 54 in the unoprostone group. The demographic characteristics of the treatment groups are presented in

Table 2. Baseline Characteristics of Study Population

	Latanoprost n = 54	Unoprostone n = 54
Gender		
Male	19	28
Female	35	26
Age (years)		
Mean ± SD	63 ± 12	62 ± 13
Range	33–81	28–88
Race		
White	33	35
Black	14	13
Hispanic	3	0
Oriental	1	0
Other	3	6
Diagnosis		
Primary open-angle glaucoma	49	48
Ocular hypertension	5	6
Previous IOP medication		
No	14	15
Yes	40	39

IOP = intraocular pressure; n = number of patients; SD = standard deviation.

Table 2. The mean age of the patients was 63 ± 13 years. There were no differences between the groups regarding gender, age, diagnosis, or previous use of ocular hypotensive medication.

Ten patients did not complete the 8-week study period, three in the latanoprost group and seven in the unoprostone group. Three of these patients (two latanoprost, one unoprostone) were lost to follow-up after the baseline visit, and no use of study medication could be documented. Thus, 52 patients in the latanoprost group and 53 in the unoprostone group were included in the ITT efficacy analysis.

Latanoprost reduced the mean IOP (mean ± standard error of the mean) by 6.7 ± 0.5 mmHg ($P < 0.001$, ANCOVA) and unoprostone reduced IOP by 3.3 ± 0.5 mmHg ($P < 0.001$, ANCOVA). The difference of 3.4 ± 0.7 mmHg between the treatments was statistically significant, in favor of latanoprost ($P < 0.001$, ANCOVA; 95% confidence interval [CI]: −4.6 to −2.1). From an adjusted overall baseline of 24.1 mmHg, the percentage reduction was 28% for latanoprost and 14% for unoprostone. The IOP-lowering effect of latanoprost and unoprostone during 8 weeks of treatment is shown in Figure 1 and Table 3.

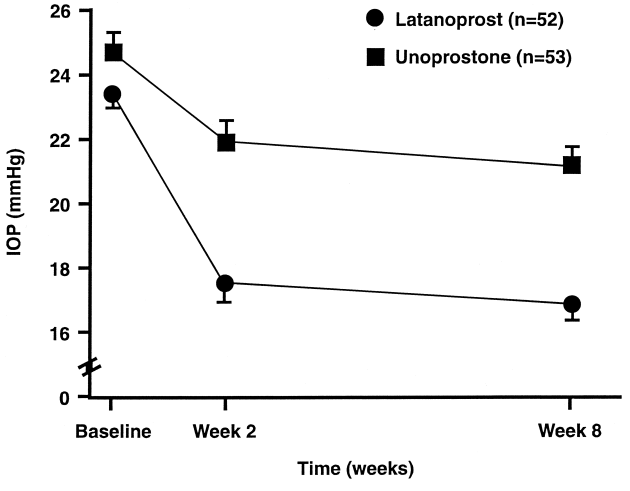

Figure 1. Mean intraocular pressure (IOP; sample mean ± standard error of the mean) based on measurements at 10:00 AM and 5:00 PM at baseline and 8-week visits and IOP measurements before noon at 2-week visit presented for each treatment group.

Table 3. Instraocular Pressure (sample mean ± SD) Measured During the Study

	Latanoprost n = 52	Unoprostone n = 53
Baseline		
10 AM	24.5 ± 3.6	25.7 ± 4.7
5 PM	22.4 ± 3.5	23.8 ± 3.8
Week 2		
Before 12 noon	17.5 ± 4.7	21.9 ± 4.8
Week 8		
10 AM	17.1 ± 4.3	21.9 ± 4.9
5 PM	16.7 ± 4.0	20.6 ± 4.5

The percentage of patients who achieved a specific IOP reduction and a specific mean IOP at 8 weeks is shown in Table 4. The proportion of patients achieving a specific IOP reduction or a specific mean IOP reduction was greater for the latanoprost group compared with the unoprostone group at all comparisons. A mean IOP of 15 mmHg or less was achieved by 33% of latanoprost patients compared with 2% of unoprostone patients. A mean IOP reduction from baseline of 30% or greater was observed in 44% of patients in the latanoprost group compared with 8% of patients in the unoprostone group. If we define clinically a nonresponder as reduction in IOP of less than 10%, then 10% of latanoprost patients and 32% of unoprostone patients fulfilled this definition.

Table 5 presents a summary of the ocular adverse events reported during this study. The most common ocular adverse event in both the latanoprost group and in the unoprostone group was ocular irritation. Nonocular adverse events were few: two events (one patient with back pain, one with tongue fissure) in the latanoprost group and two (one patient with depression, one with headache) in the unoprostone group. In addition, there was one serious adverse event of angina pectoris reported in one patient in the unoprostone group. This event was assessed as being unrelated to the use of the study medication.

Table 4. Percentage of Patients Who Achieved a Specific Mean Intraocular Pressure Reduction and a Specific Mean Intraocular Pressure at 8 Weeks

	Latanoprost n = 52	Unoprostone n = 53
Percent reduction from baseline		
≥40% mmHg	19%	2%
≥35% mmHg	33%	4%
≥30% mmHg	44%	8%
≥25% mmHg	60%	13%
≥20% mmHg	73%	28%
≥15% mmHg	79%	49%
≥10% mmHg	90%	68%
≥0% mmHg	100%	92%
Mean intraocular pressure (mmHg)		
≤15 mmHg	33%	2%
≤16 mmHg	52%	6%
≤17 mmHg	62%	13%
≤18 mmHg	67%	19%
≤19 mmHg	75%	28%
≤20 mmHg	81%	51%
≤21 mmHg	84%	62%

Table 5. Number of Ocular Findings and Symptoms Reported During 8 Weeks of Treatment with Latanoprost and Unoprostone

	Latanoprost (n = 11)	Unoprostone (n = 11)
Ocular irritation	7	3
Conjunctivitis	3	5
Conjunctival hemorrhage	1	0
Conjunctival hyperemia	0	1
Chalazion	0	1
Corneal deposits	0	1
Hypertrichosis	1	0
Iris pigmentation	1	0
Ocular trauma	0	1
Decreased visual acuity	1	1
Total	14	13

n = number of patients.

Discussion

The results of this study demonstate that latanoprost is more effective than unoprostone in reducing IOP after 8 weeks of treatment. There was a statistically significant difference in the mean IOP reduction between latanoprost and unoprostone.

Receptor-binding studies show that latanoprost has high affinity to the FP receptor, whereas the affinity of unoprostone to the FP receptor is 100-fold less potent than latanoprost (B. Resul, presented at the International Glaucoma Society meeting, Jerusalem, 1998). Latanoprost reduces IOP by increasing uveoscleral outflow,[7] and unoprostone is believed to also act by means of uveoscleral outflow.[10] The increase in uveoscleral outflow is probably FP-receptor mediated.[5] Thus, a probable explanation for the difference in effect is because of the high affinity of latanoprost to the FP receptor compared with the weaker affinity of unoprostone.[5,13]

A reduction of 30% or more in IOP has been shown to be important in halting or decreasing the rate of visual field progression in normotensive patients with glaucoma.[14] In this study of primary open-angle glaucoma and ocular hypertension, an IOP reduction 30% or greater from baseline, a marked and clinically important IOP reduction, was achieved by 44% of the latanoprost-treated patients compared with 8% of the unoprostone-treated patients. In a study by Mao et al,[15] progressive glaucomatous changes were not observed in patients whose IOP was reduced to less than 17 mmHg. In our study, IOP of less than 17 mmHg was achieved by 52% of latanoprost patients and 6% of unoprostone patients. Also, there are some studies[16,17] suggesting that an IOP of 15 mmHg or less should be the target IOP for advanced glaucomas. This IOP level was obtained in 33% of patients in the latanoprost group and in 2% of patients in the unoprostone group. Although this short-term study cannot determine which medication will prevent further progression, latanoprost was clearly more effective in reducing IOP.

The IOP-reducing effect of latanoprost has been shown to be better than timolol[1,3,4] (K. Hedman, presented at the AAO annual meeting, Chicago, 1996) or similar to timolol.[2] The IOP-reducing potential of unoprostone has been reported to be of the same magnitude as timolol.[11] Therefore, based on an indirect comparison to timolol, one could predict that latanoprost would be more effective, than unoprostone, in reducing IOP. The results of our direct comparison compare favorably with this indirect comparison. In cynomologus monkeys with laser-induced glaucoma, latanoprost was also found to be more effective than unoprostone.[10] Long-term clinical data for both latanoprost[18,19] and unoprostone[11] show that the IOP reduction is consistent over time.

Overall, latanoprost and unoprostone had a similar incidence of side effects. Changes in iris pigmentation have been reported after latanoprost[3] and unoprostone treatment.[13] In this study, increased iris pigmentation and hypertrichosis were observed using slit-lamp examination in one patient with green-brown irides in the latanoprost group. However, because the study was short term and most of the patients (80%) had homogeneously dark brown irides, one would not expect iris pigmentation to be frequently reported.

The effect of latanoprost on the blood aqueous barrier has been investigated in several studies, and no signs of blood aqueous barrier breakdown were observed.[6,20,21] In this study neither aqueous flare nor cells were detected during treatment with latanoprost and unoprostone.

In conclusion, both unoprostone and latanoprost reduced IOP from baseline and were well tolerated during 8 weeks of treatment. Latanoprost administered once daily was, however, significantly more effective in reducing IOP compared with unoprostone administered twice daily.

References

1. Alm A, Stjernschantz J. Effects on intra-ocular pressure and side effects of 0.005% latanoprost applied once daily, evening or morning. A comparison with timolol. The Scandinavian Latanoprost Study Group. Ophthalmology 1995;102:1743–52.
2. Watson P, Stjernschantz J. A six-month, randomized, double-masked study comparing latanoprost with timolol in open-angle glaucoma and ocular hypertension. The Latanoprost Study Group. Ophthalmology 1996;103:126–37.
3. Camras CB. Comparison of latanoprost and timolol in patients with ocular hypertension and glaucoma. A six-month, masked, multicenter trial in the United States. The United States Latanoprost Study Group. Ophthalmology 1996;103:138–47.
4. Mishima HK, Masuda K, Kitazawa Y, et al. A comparison of latanoprost and timolol in primary open-angle glaucoma and ocular hypertension. A 12-week study. Arch Ophthalmol 1996;114:929–32.
5. Stjernschantz J, Selén G, Sjöquist B, Resul B. Preclinical pharmacology of latanoprost, a phenyl-substituted PGF2alpha analogue. Adv Prostaglandin Thromboxane Leukot Res 1995; 23:513–8.
6. Ziai N, Dolan JW, Kacere RD, Brubaker RF. The effects on aqueous dynamics of PhXA41, a new prostaglandin F2alpha analogue, after topical application in normal and ocular hypertensive human eyes. Arch Ophthalmol 1993;111:1351–8.

7. Toris CB, Camras CB, Yablonski ME. Effects of PhXA41, a new prostaglandin F2alpha analog, on aqueous humor dynamics in human eyes. Ophthalmology 1993;100:1297–304.
8. Alm A, Widengård I, Kjellgren D, et al. Latanoprost administered once daily causes a maintained reduction of intraocular pressure in glaucoma patients treated concomitantly with timolol. Br J Ophthalmol 1995;79:12–6.
9. Yamamoto T, Kitazawa Y, Azuma I, Masuda K. Clinical evaluation of UF-021 (Rescula; isopropyl unoprostone). Surv Ophthalmol 1997;41(suppl 2):S99–103.
10. Serle JB, Podos SM, Kitazawa Y, Wang RF. A comparative study of latanoprost (Xalatan) and isopropyl unoprostone (Rescula) in normal and glaucomatous monkey eyes. Jpn J Ophthalmol 1998;42:95–100.
11. Azuma I, Masuda K, Kitazawa Y, et al. Double-masked comparative study of UF-021 and timolol ophthalmic solutions in patients with primary open-angle glaucoma or ocular hypertension. Jpn J Ophthalmol 1993;37:514–25.
12. Eisenberg DL, Camras CB. A preliminary risk-benefit assessment of latanoprost and unoprostone in open-angle glaucoma and ocular hypertension [review]. Drug Saf 1999;20:505–14.
13. Yamamoto T, Kitazawa Y. Iris-color change developed after topical isopropyl unoprostone treatment [case report]. J Glaucoma 1997;6:430–2.
14. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. Collaborative Normal-Tension Glaucoma Study Group. [published erratum appears in Am J Ophthalmol 1999;127:120]. Am J Ophthalmol 1998;126:487–97.
15. Mao LK, Stewart WC, Shields MB. Correlation between intraocular pressure control and progressive glaucomatous damage in primary open-angle glaucoma. Am J Ophthalmol 1991;111:51–5.
16. Roth SM, Spaeth GL, Starita RJ, et al. The effects of postoperative corticosteroids on trabeculectomy and the clinical course of glaucoma: five-year follow-up study. Ophthalmic Surg 1991;22:724–9.
17. Kidd MN, O'Connor M, Progession of field loss after trabeculectomy: a five-year follow-up. Br J Ophthalmol 1985;69: 827–31.
18. Watson PG. Latanoprost. Two years' experience of its use in the United Kingdom. The Latanoprost Study Group. Ophthalmology 1998;105:82–7.
19. Alm A, Widengård I. Latanoprost: experience of 2-year treatment in Scandinavia. Acta Ophthalmol Scand 2000;78:71–6.
20. Lindén C, Nuija E, Alm A. Effects on IOP restoration and blood-aqueous barrier after long term treatment with latanoprost in open angle glaucoma and ocular hypertension. Br J Ophthalmol 1997;81:370–2.
21. Diestelhorst M, Roters S, Krieglstein GK. The effect of latanoprost 0.005% once daily versus 0.0015% twice daily on intraocular pressure and aqueous humour protein concentration in glaucoma patients. A randomized, double-masked comparison with timolol 0.5%. Graefes Arch Clin Exp Ophthalmol 1997;235:20–6.