Comparison of Latanoprost with Fixed-Combination Dorzolamide and Timolol in Adult Patients with Elevated Intraocular Pressure: An Eight-Week, Randomized, Open-Label, Parallel-Group, Multicenter Study in Latin America

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ABSTRACT

Background: The newer ocular hypotensive agents available to treat glaucoma and ocular hypertension (OHT) include latanoprost, a prostaglandin $F_{2\alpha}$ analogue, and the fixed combination of dorzolamide hydrochloride, a carbonic anhydrase inhibitor, and timolol maleate, a beta-blocker.

Objective: The aim of this study was to compare the efficacy and tolerability of latanoprost with that of the fixed combination of dorzolamide and timolol over 8 weeks.

Methods: This interventional, 8-week, randomized, open-label, parallel-group study was conducted at 18 centers in 6 Latin American countries. Patients with unilateral or bilateral primary open-angle, pigmentary, or exfoliative glaucoma or OHT were randomized to receive latanoprost, 1 drop in the affected eye QD (evening), or fixed-combination dorzolamide/timolol, 1 drop in the affected eye BID (morning and evening). Medications were self-administered, 1 drop per affected eye. At baseline and week 8, intraocular pressure (IOP) was measured 3 times each at 8:30 AM, 10:00 AM, 2:00 PM, and 5:00 PM and after the water-drinking test, which estimates the IOP peak of diurnal tension curve, performed following the 5:00 PM IOP assessment. The primary efficacy outcome was change in diurnal IOP (the mean of IOP measurements) from baseline to week 8. Adverse effect (AE) data were recorded at each visit.

Results: A total of 229 patients were randomized (latanoprost, n = 112; dorzolamide/timolol, n = 117). Mean baseline diurnal IOP values were similar between the 2 groups. Mean (SD) diurnal IOP reductions at week 8 before the water-drinking test were 6.9 (3.0) mm Hg for the latanoprost group and 6.4 (3.2) mm Hg for the dorzolamide/timolol group. Mean IOP values were similar at all time points except at 5:00 PM, when levels were significantly lower in latanoprost-treated patients ($P = 0.025$). After the water-drinking test, the increase in IOP values was similar between groups at baseline but lower in latanoprost-treated patients at week 8 (adjusted difference, 1.08 mm Hg; $P = 0.012$). Fewer patients treated with latanoprost reported ocular or systemic AEs ($P = 0.025$ and $P < 0.001$, respectively).

Conclusions: In this study of patients with unilateral or bilateral primary open-angle, pigmentary, or exfoliative glaucoma or OHT IOP reductions generally were similar between treatment groups, except at 5:00 PM, when the mean IOP level was significantly lower in latanoprost-treated patients. Latanoprost was better tolerated than fixed-combination dorzolamide and timolol. (*Clin Ther.* 2004;26:755–768) Copyright © 2004 Excerpta Medica, Inc.

Key words: dorzolamide, latanoprost, ocular hypertension, open-angle glaucoma, timolol.

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INTRODUCTION

Initial medical treatment of glaucoma or ocular hypertension (OHT) focuses on decreasing and stabilizing intraocular pressure (IOP). Achieving these goals is important because IOP reductions have been associated with delayed glaucoma onset and progression,[1–3] whereas IOP fluctuations have been identified as a significant risk factor for glaucomatous progression.[4] Among the newer agents available to treat glaucoma and OHT are latanoprost, a prostaglandin $F_{2\alpha}$ analogue, and the fixed combination of dorzolamide hydrochloride, a carbonic anhydrase inhibitor, and timolol maleate, a beta-blocker.

Latanoprost 0.005%* reduces IOP by increasing uveoscleral outflow.[5–8] In patients with open-angle glaucoma or OHT, latanoprost instilled QD was found to be generally well tolerated locally and systemically and to reduce IOP more effectively than monotherapy with either timolol in 3 of 4 pivotal clinical trials[9–12] or dorzolamide.[13] In addition, latanoprost provides a smooth diurnal and nocturnal IOP curve without peaks and a consistent IOP reduction over 24 hours.[14] Extended studies[15,16] (1–2 years) have shown that patients receiving latanoprost maintain IOP reductions without upward drift and without serious systemic adverse effects (AEs).

The fixed combination of dorzolamide 2% and timolol maleate 0.5%† instilled BID has been shown to be more effective in decreasing IOP than either drug administered alone; both agents reduce aqueous humor secretion.[17–19] The safety profile of the dorzolamide/timolol combination reflects its 2 components. The most commonly reported ocular AEs are burning and/or stinging on instillation.[18,19] However, systemic absorption can lead to systemic beta-adrenergic blockade and may aggravate obstructive pulmonary disease,[20] congestive heart failure,[21] and atrioventricular block.[22,23] In addition, caution must be used in some patients receiving other therapeutic agents; interactions have been reported between beta-blockers and calcium antagonists,[24] catecholamine-depleting drugs,[25] digoxin,[26] and quinidine[27] and may produce AEs.

Previous research[28–32] has shown that latanoprost QD monotherapy decreases IOP at least as effectively as BID administration of either the unfixed or fixed combination of dorzolamide and timolol. The present study was designed to further compare the efficacy and tolerability of latanoprost instilled QD with that of the fixed combination of dorzolamide and timolol administered BID in patients with glaucoma or OHT. The ability of the treatments to control IOP fluctuations also was assessed using the water-drinking test,[33,34] which induces an episodic increase in IOP after rapid consumption of 1 L of water.

PATIENTS AND METHODS

Study Design

This interventional, 8-week, randomized, open-label, parallel-group study was conducted at 18 centers in 6 Latin American countries. Patients were enrolled between January and April 2002. An institutional review board or independent ethics committee for each study site approved the protocol, and the study was performed in accordance with the ethical standards adopted by the 1964 18th World Medical Assembly in Helsinki, Finland, as well as with later revisions.

Patient Selection

Patients aged ≥18 years with unilateral or bilateral primary open-angle, pigmentary, or exfoliative glaucoma or OHT (IOP ≥ 21 mm Hg at diagnosis) and whose best-corrected visual acuity (Snellen) was ≥20/80 were eligible. All patients were required to be receiving ocular hypotensive monotherapy or dual therapy at screening or to have received such therapy during the previous year. At baseline, a mean 8:30 AM IOP ≥21 mm Hg for patients with glaucoma or ≥25 mm Hg for patients with OHT was required for randomization.

Patients were excluded from the study if they had a history of any of the following: acute angle closure; closed or barely open anterior chamber angle; ocular filtering surgery (the unfiltered eye might be eligible); argon laser trabeculoplasty, ocular surgery, or inflammation or infection within 3 months prior to screening; hypersensitivity to benzalkonium chloride, sulfonamides, or any other component of a study medication; any condition in which treatment with a beta-blocker is contraindicated; or any other abnormal or ocular condition or symptom that, in the judgment of the investigator, would prevent study partic-

*Trademark: Xalatan® (Pfizer Inc, New York, New York).
†Trademark: Cosopt® (Merck & Co., Inc., West Point, Pennsylvania).

ipation. Use of systemic medication known to affect IOP prevented the patient from entering the study unless the patient's condition and the medication dosage were stabilized for 3 months prior to the screening visit and the dosage was not expected to change during the study. Patients were not eligible if they had used any investigational medication within 30 days prior to the screening visit. Women of childbearing potential not using adequate contraception and pregnant, possibly pregnant, or breastfeeding women also were excluded from the study.

Prior to inclusion in the study, investigators at each study center provided patients with full and adequate verbal and written information regarding the objectives and procedures of the trial and the possible risks involved, and all patients provided written informed consent to participate.

Methods

Up to 4 weeks prior to baseline, patients underwent a screening visit, which included a review of the patient's medical and ocular histories and recording of demographic data, concomitant medications, and diseases. Best-corrected visual acuity and refraction, visual field testing (unless performed and documented within the previous year), ophthalmoscopy, and lid and slit-lamp (biomicroscopy) examinations were conducted, and IOP was measured using a calibrated Goldmann applanation tonometer. At the screening visit, each patient's blood pressure (BP) and heart rate (HR) were measured. Within 3 days of the screening visit, spirometry and 12-lead electrocardiography (ECG) were performed. Resting HR was recorded for 60 seconds after a supine resting period of 60 seconds. Arterial BP was recorded using a standard mercury sphygmomanometer; diastolic BP was recorded at the Korotkoff V sound. All measurements were performed and recorded by an investigator or trained staff member.

Following screening, eligible patients began the required washout periods for current ocular medication as follows: 4 weeks for beta-blockers and prostaglandin analogues, 2 weeks for adrenergic agonists, and 5 days for cholinergic agonists and carbonic anhydrase inhibitors. Patients whose ocular hypertensive therapy required a 4-week washout period had an additional safety check visit 2 weeks prior to baseline. If at the time of the safety visit a patient's IOP had increased to a level thought to be detrimental, the patient was withdrawn from the study at the discretion of the investigator.

Patients underwent 3 additional study visits: at baseline (randomization) and after 2 and 8 weeks of therapy. For each patient, the same unmasked examiner measured the IOP using the same calibrated Goldmann applanation tonometer at each study visit; measurements were performed before pupils were dilated. IOP was measured at any time during the day at the screening, safety check, and week-2 visits. At baseline and week 8, IOP was measured 3 times each at 8:30 AM (before study medication was instilled at week 8), 10:00 AM, 2:00 PM, and 5:00 PM; the means of the 3 measurements were used in efficacy analyses. BP and HR also were monitored at each study visit; it was preferred that the same examiner perform the same assessment for each patient at each visit. At baseline and week 8, patients underwent lid and slit-lamp examinations, assessments of best-corrected visual acuity, spirometry (3 readings), and ECG. Ophthalmoscopy also was performed at week 8. The water-drinking test, which estimates the IOP peak of the diurnal tension curve,[33,34] was performed at baseline and week 8; patients had no beverages after 1:00 PM and drank 1 L of water in ~5 minutes following the 5:00 PM IOP measurement. IOP was measured in each eye at 5:15 PM, 5:30 PM, and 5:45 PM, and the highest of these 3 measurements was used to calculate IOP elevation after drinking water.

At the baseline visit, patients randomly were assigned within each investigative site in a 1:1 ratio to receive either latanoprost 0.005% or the fixed combination of dorzolamide 2% and timolol 0.5%. Randomization envelopes indicating treatment assignment were provided to each site, and patient numbers were assigned sequentially. All patients were issued 2 bottles of study medication. Those in the latanoprost group were instructed to instill 1 drop in the affected eye(s) QD at 8:00 PM beginning on the baseline day, and those in the dorzolamide/timolol group were instructed to instill 1 drop in the affected eye(s) BID at 8:00 AM and 8:00 PM beginning with the 8:00 PM dose on the baseline day. No other IOP-reducing therapy was permitted. At the week-2 visit, patients were issued 1 or 2 bottles of study medication (depending on whether the patient had started the second bottle dispensed at baseline) and were reminded to change

medication bottles every 2 weeks. Although medication bottles were supplied in an open-label fashion, evaluators conducting spirometry and ECG assessments were masked to treatment assignment. Treatment was discontinued at any time if the investigator believed it was medically necessary or if it was the wish of the patient. Patients who became pregnant also were withdrawn from the study.

AEs, defined as any undesirable event occurring in a patient, were monitored by investigators carefully throughout the study. Investigators reported all directly observed AEs and all AEs reported spontaneously by the patient. At each study visit, investigators also queried patients about any health problems. Beginning with the first dose of medicine, each AE was classified by the investigator as serious or nonserious and was recorded by intensity (mild, moderate, or severe), regardless of its relationship to treatment. At the end of the treatment period, any patient with a serious AE, an AE related to study medication, or an ocular AE was followed up 2 weeks after the final visit. All patients with ongoing serious AEs or nonserious AEs considered to be related to study medication were followed up until the AEs resolved or were considered as chronic or stable.

Efficacy and Tolerability Analyses

The primary efficacy end point was the mean change in diurnal IOP from baseline to week 8, with diurnal IOP calculated as the mean of IOP measurements taken at 8:30 AM, 10:00 AM, 2:00 PM, and 5:00 PM. Secondary efficacy end points included the following: (1) IOP changes from baseline to week 8 measured at 8:30 AM, 10:00 AM, 2:00 PM, and 5:00 PM; (2) proportions of patients reaching specific IOP levels by week 8; (3) changes in maximum IOP and IOP fluctuations from baseline to week 8; and (4) IOP elevations following the water-drinking test. The study also compared groups with regard to ocular and systemic tolerability variables, including cardiovascular and respiratory effects. End points were the proportion of patients with either a ≥10% relative reduction in HR, any degree of atrioventricular conduction delay, or sinus bradycardia at week 8.

Patients requiring bilateral IOP-reducing therapy were treated in both eyes, but only the eye that met all inclusion and no exclusion criteria was designated a study eye. If both eyes qualified, the worse eye, as judged by the investigator, was designated as the study eye and was included in both efficacy and tolerability analyses. The contralateral (treated) eye also was included in tolerability analyses.

Intent-to-treat (ITT) analyses included all randomized patients who received study medication and had ≥1 valid IOP assessment after starting treatment. If any IOP measurement was missing at the week-8 visit, the diurnal IOP was calculated as the mean of available measurements at that visit; if all week-8 IOP measurements were missing, the week-2 IOP level was carried forward. Per-protocol (PP) analyses included patients who completed the study without a major protocol violation. No imputation of missing values was performed for PP analyses. Analyses of IOP elevation after drinking water were based on observed values.

The statistical significance of within- and between-group IOP changes from baseline was tested using the paired *t* test and the *t* test, respectively. The analysis of covariance (ANCOVA) model, with baseline IOP as the covariate and treatment and centers as factors, was used to further compare treatment groups in their mean IOP change from baseline to week 8; 95% CIs were calculated based on ANCOVA. Numbers and proportions of patients achieving specified percentages of IOP reduction and specified mean IOP levels at the end of treatment were calculated. The range of IOP levels and the highest IOP level measured during the day before the water-drinking test were summarized, providing a diurnal tension assessment. Within-group changes in IOP elevation since baseline and between-group differences in IOP elevation and change since baseline were tested (paired *t* test and *t* test, respectively). In addition, the ANCOVA model was used to compare IOP elevations after the water-drinking test at week 8 using baseline increase in IOP and IOP before drinking water as covariates. All statistical tests were 2-tailed and were performed at the 5% significance level. Statistical calculations were performed using SAS software version 6.0 (SAS Institute Inc., Cary, North Carolina).

All patients who received ≥1 dose of study medication were included in tolerability analyses. Frequency of AEs was summarized by body system and was standardized using *Medical Dictionary for Regulatory Activities* (MedDRA®, International Federation of Pharmaceutical Manufacturers Associations[35]) terms. HR, PR interval, QRS duration, and BP were summa-

rized by visit and examined for within-group and between-group differences at weeks 2 and 8. In addition, numbers of patients with bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second- or third-degree atrioventricular block, overt cardiac failure, or cardiogenic shock were summarized by visit. Between-group differences in patients who developed any cardiovascular or pulmonary problems after treatment were analyzed using the Fisher exact test.

Prior to initiating the study, it was determined that a sample size of at least 87 patients per treatment group was required to detect a difference of 1.5 mm Hg in mean diurnal IOP reduction between treatment groups at a significance of 0.05, with a power of 80%, and assuming a standard deviation of 3.5 mm Hg. To allow for withdrawals, we planned to recruit a total of 200 patients.

RESULTS

A total of 229 patients were included in this study. At baseline, 112 patients were randomized to receive latanoprost and 117 to receive the fixed combination of dorzolamide and timolol (**Table I**). One patient in the latanoprost group was lost to follow-up prior to any postbaseline assessment and was excluded from ITT analyses. Both eyes were treated in 78/111 patients (70.3%) in the latanoprost group and in 67/117 patients (57.3%) treated with dorzolamide/timolol.

No statistically significant differences were found between treatment groups with respect to demographic and patient characteristics (**Table II**). Withdrawal from the study occurred in 8/112 patients (7.1%) treated with latanoprost and in 7/117 patients (6.0%) receiving dorzolamide/timolol (Table I). Included in the PP population were 98 patients (87.5%) in the latanoprost group and 101 patients (86.3%) in the dorzolamide/timolol group. The exclusions were due primarily to sinus bradycardia at screening or baseline (9 patients in each group) and inadequate IOP at baseline (2 patients in each group).

Table I. Disposition of the study patients (N = 229). (Values are presented as no. [%] of patients.)

	Latanoprost	Dorzolamide/ Timolol
Total randomized	112 (100.0)	117 (100.0)
Completed study	104 (92.9)	110 (94.0)
Withdrew from study	8 (7.1)	7 (6.0)
Reasons for withdrawal		
Protocol violation	2 (1.8)	3 (2.6)
Consent withdrawn	1 (0.9)	0 (0.0)
Loss to follow-up	1 (0.9)	0 (0.0)
Adverse event	0 (0.0)	2 (1.7)
Other	4 (3.6)	2 (1.7)

Table II. Baseline demographic and clinical characteristics of the intent-to-treat population (N = 228).* (Values are expressed as no. [%] of patients unless otherwise indicated.)

Characteristic	Latanoprost (n = 111)	Dorzolamide/ Timolol (n = 117)
Age, y		
Mean (SE)	60.1 (10.9)	61.1 (11.7)
Range	27–89	18–84
Sex		
Women	78 (70.3)	70 (59.8)
Men	33 (29.7)	47 (40.2)
Race		
Hispanic	43 (38.7)	44 (37.6)
White	32 (28.8)	32 (27.4)
Mixed/multiracial	30 (27.0)	29 (24.8)
Black	6 (5.4)	9 (7.7)
Asian	0 (0.0)	2 (1.7)
Other	0 (0.0)	1 (0.9)
Diagnosis in study eye(s)		
Primary open-angle glaucoma	76 (68.5)	91 (77.8)
Ocular hypertension	23 (20.7)	17 (14.5)
Exfoliative glaucoma	7 (6.3)	6 (5.1)
Pigmentary glaucoma	5 (4.5)	3 (2.6)
Duration of condition of study eye(s), mo		
<6	17 (15.3)	23 (19.7)
6–36	44 (39.6)	42 (35.9)
>36–120	43 (38.7)	37 (31.6)
>120	7 (6.3)	15 (12.8)
Family history of glaucoma/ocular hypertension	27 (24.3)	36 (30.8)
Visual field, any glaucomatous defect in study eye(s)	75 (67.6)	91 (77.8)

*No significant between-group differences were found. Percentages may not total 100 due to rounding.

Efficacy

Because ITT and PP efficacy analyses yielded similar results, we report only ITT findings. At baseline, the mean (SD) diurnal IOP was 23.5 (2.8) mm Hg in the patients treated with latanoprost versus 23.6 (3.3) mm Hg in the dorzolamide/timolol group (**Table III**). After 8 weeks of therapy, mean diurnal IOP values were 16.6 (3.0) mm Hg in latanoprost-treated and 17.2 (3.1) mm Hg in dorzolamide/timolol-treated patients; the differences were not statistically significant. Mean diurnal IOP reductions at week 8 were 6.9 (3.0) mm Hg for the latanoprost group (a 29.3% reduction) and 6.4 (3.2) mm Hg for the dorzolamide/timolol group (a 26.5% reduction); the differences were not statistically significant. The adjusted difference between groups (ANCOVA) also was not statistically significant (0.58 mm Hg; 95% CI, –0.10 to 1.26).

Mean IOP values at each time point were similar between groups at baseline (Table III; **Figure 1**). At week 8, the latanoprost group showed slightly higher IOP reductions than the dorzolamide/timolol group, but the differences reached statistical significance only at 5:00 PM (adjusted difference [ANCOVA], 0.84 mm Hg; 95% CI, 0.10 to 1.57; $P = 0.025$). **Figure 2** illustrates percentages of patients who achieved specific diurnal IOP levels after 8 weeks of treatment.

Baseline diurnal variations prior to the water-drinking test were similar between the 2 groups of patients, with no significant difference between the mean maximum IOP (latanoprost, 25.6 [3.0] mm Hg; dorzolamide/timolol, 25.8 [3.9] mm Hg) or the mean IOP range (latanoprost, 4.2 [2.2] mm Hg; dorzolamide/timolol, 4.4 [2.8] mm Hg). Following the baseline water-drinking test, the increase in IOP was not significantly different between the 2 groups (latanoprost, 5.8 [3.5] mm Hg; dorzolamide/timolol, 5.5 [3.8] mm Hg) (**Table IV**). However, at 8 weeks of treatment, a significant difference was found between the 2 groups in response to the water-drinking test. Following water drinking, the latanoprost group had a smaller increase in IOP than did the dorzolamide/timolol group (5.4 [3.7] mm Hg vs 6.3 [3.2] mm Hg, respectively; $P = 0.045$) and a smaller mean value of maximum IOP (21.5 [5.0] mm Hg vs 23.5 [4.4] mm Hg, respectively; $P = 0.003$). The estimated mean difference in IOP elevation between the 2 groups using ANCOVA was 1.08 mm Hg (95% CI, 0.24 to 1.93; $P = 0.012$). The latanoprost group achieved a significantly greater reduction from baseline in mean maximum IOP values following the water-drinking test at

Table III. Intraocular pressure (IOP) and IOP reduction (mm Hg) from baseline to week 8 in the intent-to-treat population (N = 228). (Values are expressed as unadjusted mean [SD].)

	IOP, mm Hg		IOP Reduction, mm Hg	
Time Point	Latanoprost (n = 111)	Dorzolamide/Timolol (n = 117)	Latanoprost (n = 111)	Dorzolamide/Timolol (n = 117)
Baseline				
8:30 AM	25.1 (2.9)	25.0 (3.6)	–	–
10:00 AM	24.0 (3.2)	24.1 (3.9)	–	–
2:00 PM	22.5 (3.3)	22.7 (3.5)	–	–
5:00 PM	22.4 (3.4)	22.6 (4.0)	–	–
Diurnal	23.5 (2.8)	23.6 (3.3)	–	–
Week 8				
8:30 AM	16.8 (3.2)	17.5 (3.7)	8.2 (3.4)	7.4 (3.5)
10:00 AM	16.6 (3.2)	17.1 (3.7)	7.3 (3.8)	7.0 (3.8)
2:00 PM	16.0 (3.0)	16.7 (3.1)	6.4 (3.6)	6.0 (3.9)
5:00 PM	16.1 (2.9)	17.1 (3.1)	6.1 (3.3)*	5.4 (4.2)
Diurnal	16.6 (3.0)	17.2 (3.1)	6.9 (3.0)	6.4 (3.2)

*$P = 0.025$ for adjusted difference versus dorzolamide/timolol (analysis of covariance).

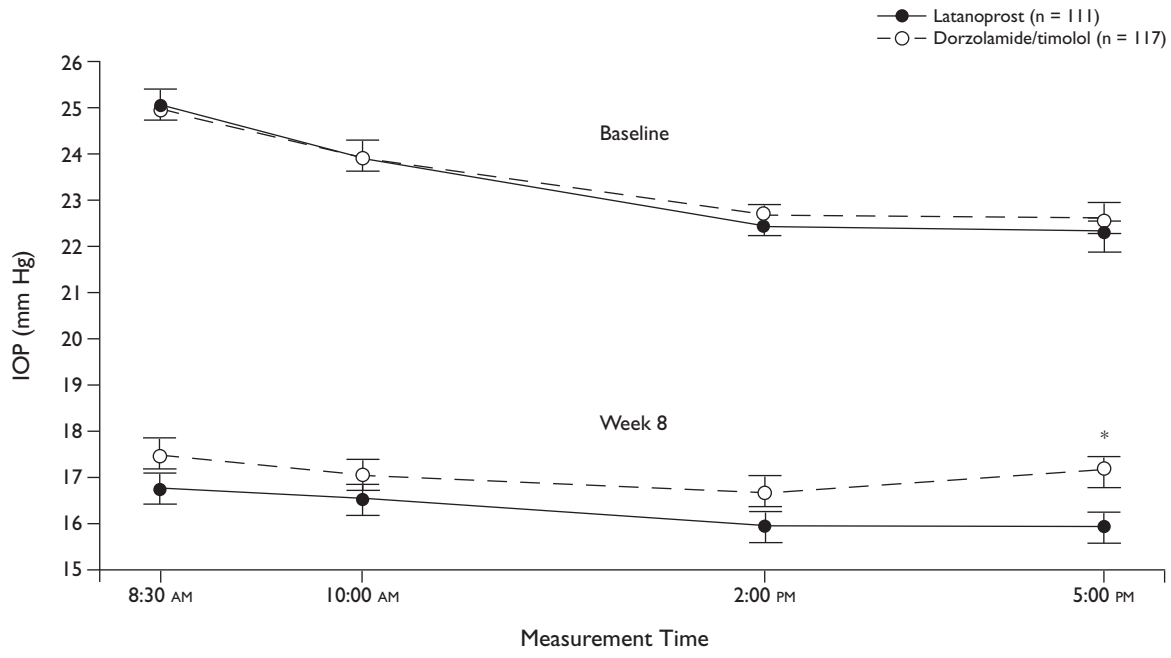

Figure 1. Unadjusted mean intraocular pressure (IOP) (SEM) in the intent-to-treat population (N = 228). $^{*}P = 0.025$ for the adjusted difference versus dorzolamide/timolol.

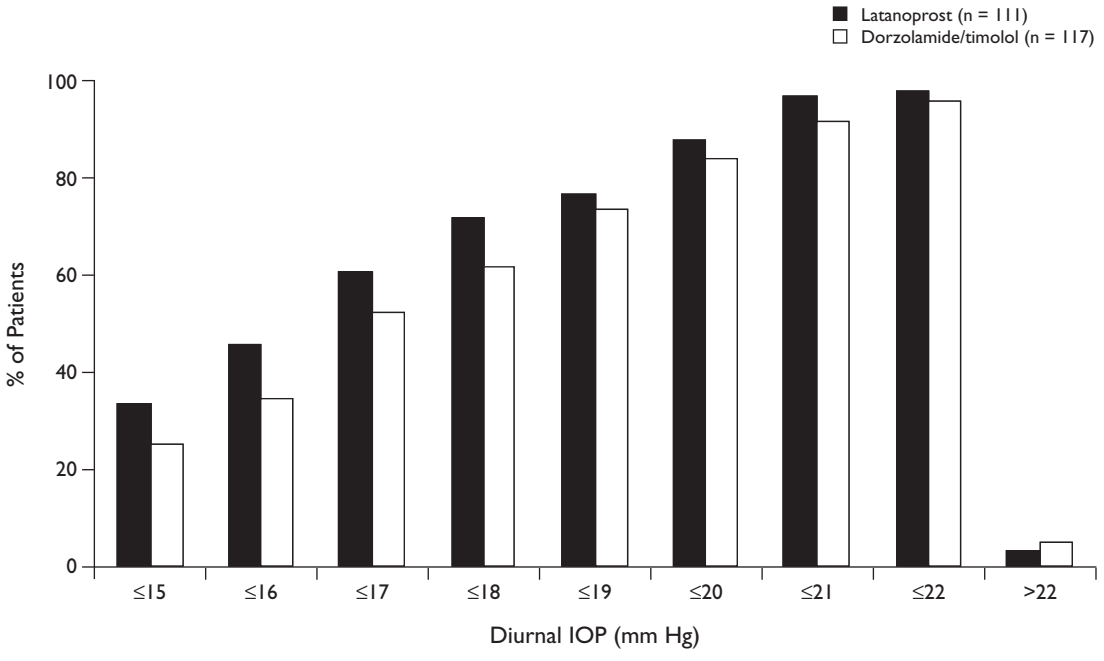

Figure 2. Percentages of patients in the intent-to-treat population (N = 228) achieving specific diurnal intraocular pressure (IOP) at week 8. No significant between-group differences were found.

Table IV. Summary of intraocular pressure (IOP) (mm Hg) before and after water-drinking test in the intent-to-treat population (N = 228).

	Latanoprost		Dorzolamide/Timolol	
Time Point/IOP	Unadjusted Mean (SD)	Range	Unadjusted Mean (SD)	Range
Baseline*				
Before drinking water	22.4 (3.4)	14.3 to 31.3	22.6 (4.0)	11.3 to 35.0
Maximum after drinking water	28.2 (5.1)	20.0 to 46.0	28.0 (5.8)	18.0 to 50.0
Increase	5.8 (3.5)	–0.3 to 18.7	5.5 (3.8)	–1.7 to 17.0
Week 8†				
Before drinking water	16.1 (2.9)	10.0 to 22.7	17.1 (3.1)	10.7 to 24.7
Maximum after drinking water	21.5 (5.0)	12.0 to 50.0	23.5 (4.4)‡	12.0 to 35.0
Increase	5.4 (3.7)	–1.0 to 29.0	6.3 (3.2)§	0.0 to 14.3

*No. of patients: latanoprost, 111; dorzolamide/timolol, 117.
†No. of patients: latanoprost, 109; dorzolamide/timolol, 114.
‡$P = 0.003$ versus latanoprost (independent-samples *t* test).
§$P = 0.045$ versus latanoprost (independent-samples *t* test).

week 8 than did the dorzolamide/timolol group (6.5 [4.6] mm Hg [22.6%] vs 4.6 [5.3] mm Hg [14.6%], respectively; $P = 0.005$). Although proportions of patients reaching specific percentage IOP elevations following the water-drinking test were similar at baseline, latanoprost-treated patients had significantly lower elevations at the 35% and 40% levels at week 8 ($P < 0.05$ for both) (**Figure 3**).

Tolerability

At least 1 AE was reported by 49/229 patients (21.4%) randomized to study medication, including 10/112 patients (8.9%) from the latanoprost group and 39/117 patients (33.3%) in the dorzolamide/timolol group (**Table V**). Ocular AEs (mainly eye irritation, eye pain, and conjunctival disorder) were reported by 4 latanoprost-treated patients (3.6%) and by 14 dorzolamide/timolol-treated patients (12.0%) ($P = 0.025$). Systemic AEs were more common in the dorzolamide/timolol group than in the latanoprost group (29 [24.8%] vs 8 [7.1%], respectively; $P < 0.001$). Systemic AEs reported more often by those receiving dorzolamide/timolol included bradycardia, sinus bradycardia, chest pain, taste disturbance, and dizziness. AEs considered related to study medication also were reported by more dorzolamide/timolol- than latanoprost-treated patients (29 [24.8%] vs 6 [5.4%], respectively; $P < 0.001$). The most frequently reported such events in dorzolamide/timolol-treated patients were bradycardia/sinus bradycardia (14 [12.0%]); 2 latanoprost-treated patients (1.8%) reported these conditions ($P < 0.01$ between groups). In the dorzolamide/timolol group, 3 patients (2.6%) reported serious AEs (pneumonia and urinary tract infection in 1 patient; hyperglycemia and liver cancer in 1 patient each); none were considered to be related to study medication. Two patients (1.7%) in the dorzolamide/timolol group withdrew from the study due to conjunctivitis and ocular irritation (1 patient each). No latanoprost-treated patient reported a serious AE or withdrew from the study due to an AE.

A summary of vital signs measured at baseline and at weeks 2 and 8 is provided in **Table VI**. The mean change in HR from baseline in dorzolamide/timolol-treated patients was –3.7 bpm and –5.9 bpm at weeks 2 and 8, respectively (both, $P < 0.001$). Mean changes in HR from baseline were small in latanoprost-treated patients, and the difference between the latanoprost and dorzolamide/timolol groups was significant at week 8 ($P < 0.001$). In addition, a significant change from baseline to week 8 occurred in the PR interval seen on ECG in dorzolamide/timolol-treated patients ($P = 0.032$),

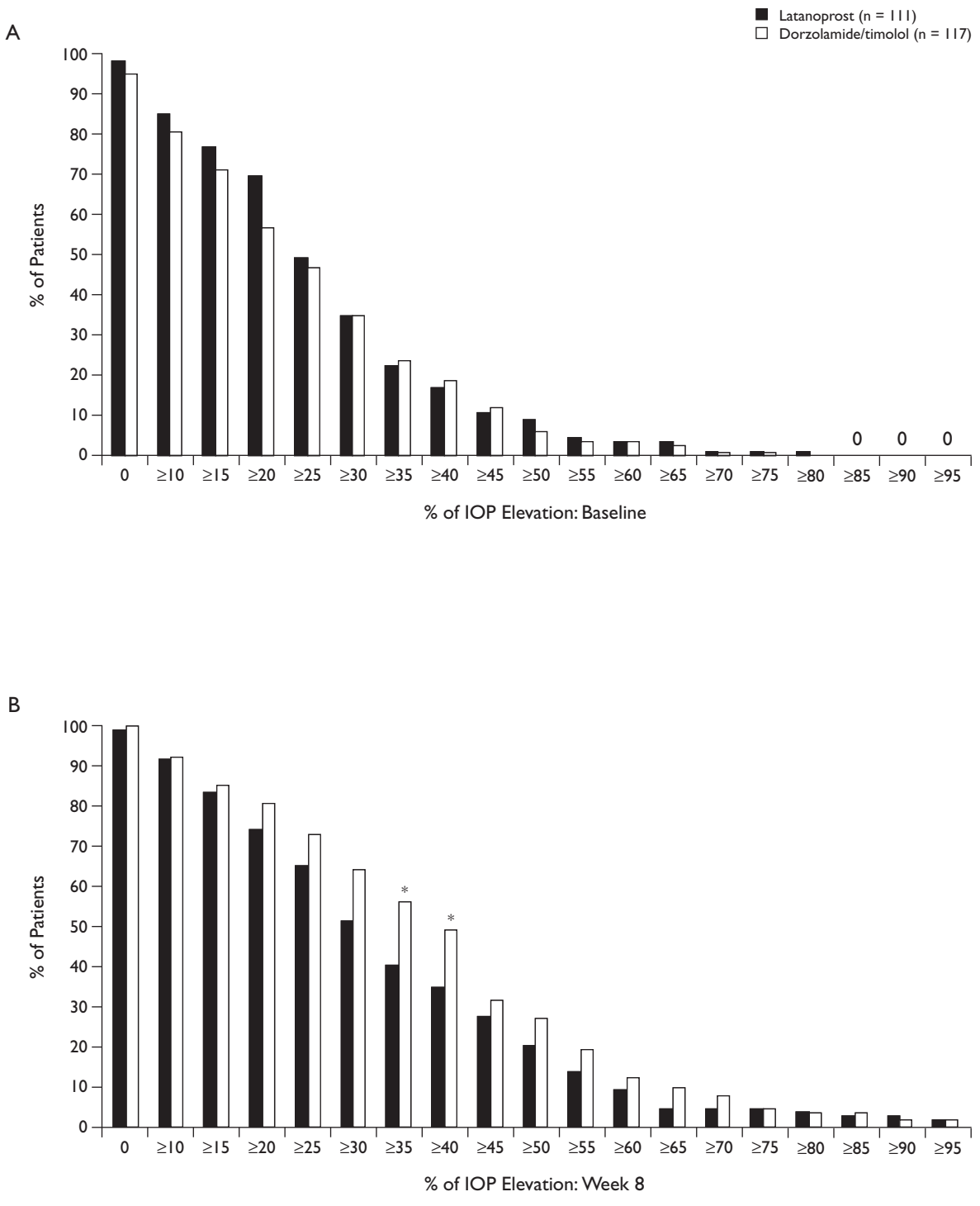

Figure 3. Percentages of patients who reached specific percentages of intraocular pressure (IOP) elevation after the water-drinking test at baseline (A) and week 8 (B) in the intent-to-treat population (N = 228). $^{*}P < 0.05$ versus latanoprost.

Table V. Tolerability profile of the study drugs in the randomized population (N = 229). (Values are expressed as no. [%] of patients.)

	Latanoprost (n = 112)	Dorzolamide/Timolol (n = 117)
No AEs*	102 (91.1)	78 (66.7)
Ocular AE(s)†	4 (3.6)	14 (12.0)
Systemic AE(s)*	8 (7.1)	29 (24.8)
AE(s) related to study medication*	6 (5.4)	29 (24.8)
Discontinuation due to AE(s)	0 (0.0)	2 (1.7)‡

AEs = adverse events.
*$P < 0.001$ between groups.
†$P = 0.025$ between groups.
‡Due to conjunctivitis and ocular irritation (1 patient each).

although the difference between treatment groups was not significant. An analysis of patients with any new significant findings related to pulmonary or cardiovascular functions excluded 22 patients with an HR <60 bpm or other significant findings at screening or baseline. Two additional patients were excluded because they were not assessed at their final visit. At week 8, significantly more patients in the dorzolamide/timolol group than in the latanoprost group had developed sinus bradycardia (11/104 [10.6%] vs 1/100 [1.0%], respectively; $P = 0.005$) or had a relative reduction in HR of ≥10% (46/104 [44.2%] vs 21/100 [21.0%], respectively; $P = 0.001$).

DISCUSSION

After 8 weeks of treatment and following washout of previous ocular hypotensive therapy, latanoprost as monotherapy administered QD reduced IOP as effectively as the fixed combination of dorzolamide and timolol instilled BID. Compared with baseline, reductions in mean diurnal IOP levels were 29.3% and 26.5%, respectively. IOP reductions were similar between groups at most time points, reaching statistical significance in favor of latanoprost at 5:00 PM. These findings parallel results of a 3-month study[30] conducted in 226 patients with glaucoma and IOP levels that were insufficiently controlled by timolol alone who were randomly assigned to receive either latanoprost monotherapy or the fixed combination of dorzolamide and timolol. Reductions from baseline in mean diurnal IOP levels were 19% and 17%, respectively, and significant differences in mean IOP levels were seen at 5:00 PM but not at 10:00 AM. IOP levels measured at 10:00 AM in both studies represent the peak effects (2 hours postdose) of dorzolamide while IOP levels at

Table VI. Vital signs at baseline and weeks 2 and 8 in the randomized population (N = 229). (Values are expressed as mean [SD].)

	Baseline		Week 2		Week 8	
Parameter	Latanoprost	Dorzolamide/Timolol	Latanoprost	Dorzolamide/Timolol	Latanoprost	Dorzolamide/Timolol
SBP, mm Hg	135.3 (19.1) (n = 111)	135.3 (17.0) (n = 117)	137.7 (19.5) (n = 110)	133.5 (18.6) (n = 116)	137.2 (17.9) (n = 108)	133.6 (16.0) (n = 115)
DBP, mm Hg	82.2 (9.9) (n = 111)	83.1 (9.9) (n = 117)	83.1 (11.3) (n = 110)	81.2 (12.6) (n = 116)	83.0 (8.6) (n = 108)	81.5 (9.8) (n = 115)
HR, bpm	74.6 (12.2) (n = 111)	72.5 (10.4) (n = 117)	73.6 (9.5) (n = 110)	68.9 (9.0)* (n = 116)	73.2 (9.9) (n = 109)	66.6 (10.2)*† (n = 115)
PR interval, s	0.16 (0.03) (n = 112)	0.16 (0.02) (n = 117)	NM	NM	0.16 (0.03) (n = 109)	0.17 (0.02)‡ (n = 114)
QRS duration, s	0.08 (0.06) (n = 112)	0.09 (0.07) (n = 117)	NM	NM	0.08 (0.02) (n = 109)	0.08 (0.02) (n = 115)

SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; NM = not measured.
*$P < 0.001$ versus baseline.
†$P < 0.001$ between groups.
‡$P = 0.032$ versus baseline.

5:00 PM were measured at the time of approximate trough effect of the drugs.[36,37] These findings suggest that although both therapies effectively reduce IOP levels, latanoprost might provide slightly more IOP reduction at the end of the day. Latanoprost previously has been reported to more effectively maintain a uniform circadian IOP reduction than either dorzolamide or timolol.[38]

Supporting these findings of consistent control of IOP levels by latanoprost, in the present study we found that patients who received latanoprost had smaller elevations in IOP levels following the water-drinking test, which was administered at the time of trough effect of all agents. The spike in IOP induced by drinking water has been found to correlate strongly with the peak pressure of an individual's diurnal variation.[39] A substantial rise in IOP in response to the water-drinking test has been identified as a risk factor for disease progression.[40,41] It can be speculated that the dampening effect on IOP elevation in latanoprost-treated patients after drinking water may reflect this agent's mechanism of action (ie, an increase in uveoscleral outflow). Both dorzolamide and timolol decrease IOP by reducing aqueous humor secretion.

Although the short duration of the present study did not allow comparison of disease progression between treatment groups, others[4,42–44] have linked diurnal IOP instability to glaucoma progression. For example, in 64 patients with open-angle glaucoma who used home tonometry to monitor their IOP levels for 5 days, diurnal IOP range and IOP range over measurement days predicted disease progression while baseline IOP did not.[4] The authors concluded that large fluctuations in diurnal IOP (in the upper quartile of the range) constitute a significant risk factor in these patients. Home tonometry also was used in a study[42] that found that 29% of patients with apparently controlled IOP levels and progressive visual field loss had IOP peaks compared with 5% of patients with stable visual fields. In patients with primary open-angle glaucoma and complete cupping of the optic disc who were followed for ≥5 years, variability in individual IOP measurements was lower in those with stable vision compared with those having decreased vision (4.5 mm Hg vs 9.0 mm Hg, respectively; $P < 0.001$).[43] Finally, visual field decay also has been correlated with IOP variation (range and peak) in newly diagnosed patients with high-pressure open-angle glaucoma.[44]

By design, the present study excluded patients in whom treatment with a beta-blocker was contraindicated, such as patients with a history or evidence of bradycardia and/or asthma. This exclusion criterion and others may have resulted in a patient population somewhat healthier than might be expected in a general ophthalmic clinic population. Despite this limitation, latanoprost-treated patients exhibited significantly better systemic and ocular safety profiles than did those receiving the fixed combination of dorzolamide and timolol. Twelve percent of patients treated with dorzolamide and timolol reported bradycardia/sinus bradycardia versus 1.8% of patients treated with latanoprost, a substantially higher proportion than would be expected based on the manufacturer's prescribing information,[45] which indicates that bradycardia occurs in <1% of patients. Although fewer AEs might be expected when administering 1 rather than 2 ocular hypotensive agents, long-term effects sometimes associated with latanoprost use, such as hyperpigmentation[46] or hypertrichosis,[47] might not have developed because of the short duration (8 weeks) of the study.

CONCLUSIONS

In this study of patients with unilateral or bilateral primary open-angle, pigmentary, or exfoliative glaucoma or OHT, IOP reductions after 8 weeks of treatment were similar between patients receiving latanoprost or dorzolamide/timolol for the diurnal measure and at most time points, reaching statistical significance in favor of latanoprost at 5:00 PM. Latanoprost monotherapy QD was better tolerated than BID treatment with the fixed combination of dorzolamide and timolol.

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