A Randomized Double-masked Crossover Study Comparing Latanoprost 0.005% With Unoprostone 0.12% in Patients With Primary Open-angle Glaucoma and Ocular Hypertension

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• PURPOSE: To compare the intraocular pressure)–lowering effect and side effects of latanoprost 0.005% once daily with unoprostone 0.12% twice daily.

• METHODS: Sixty patients with primary open-angle glaucoma or ocular hypertension were randomized to receive either latanoprost once daily in the evening and placebo once daily in the morning, or unoprostone twice daily in the morning and evening. The study was double masked and followed a crossover design with two treatment periods of 1 month separated by a 3-week washout period. The intraocular pressure was measured at 9 AM and 5 PM on the baseline and day 28 visits, and at 9 AM on day 2 and day 14 visits of each treatment period. The 9 AM measurement was taken 2 hours and 13 hours after the last drop of unoprostone and latanoprost, and the 5 PM measurement was at 10 and 21 hours, respectively. The mean of the measurements was calculated. Safety parameters were also recorded.

• RESULTS: Fifty-six patients completed both treatment periods and had intraocular pressure data available for evaluation. After 1 month of treatment, latanoprost significantly reduced intraocular pressure (mean ± SEM) by 6.1 ± 0.5 mm Hg ($P < .001$) and unoprostone by 4.2 ± 0.4 mm Hg ($P < .001$) adjusted from an overall baseline of 22.3 ± 0.5 mm Hg and 23.2 ± 0.4 mm Hg, respectively. The difference of 1.9 mm Hg between treatments was statistically significant in favor of latanoprost [$P = .003$, analysis of covariance (ANCOVA)]. Unadjusted analysis of responders using the percentage decrease in intraocular pressure showed that the proportion of responders in the latanoprost-treated group was greater than in the unoprostone-treated group. Adverse ocular symptoms and findings were mild in both treatment groups. Eye redness and ocular irritation were the most frequently reported events.

• CONCLUSIONS: Latanoprost once daily was significantly more effective in reducing intraocular pressure compared with unoprostone twice daily after 1 month of treatment in patients with primary open-angle glaucoma and ocular hypertension. Both drugs were well tolerated with few ocular adverse events. (Am J Ophthalmol 2001;131:636–642. © 2001 by Elsevier Science Inc. All rights reserved.)

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THERAPEUTIC REGIMENS FOR GLAUCOMA HAVE changed dramatically in the last few years, with increasingly effective glaucoma therapies with fewer side effects and convenient dose schedules becoming available. These include prostaglandin analogues, such as latanoprost and unoprostone. Latanoprost, a prostaglandin $F_{2\alpha}$ analog, has proven to be an effective ocular hypotensive drug.[1–7] Its main mechanism for reducing intraocular pressure is an increase in the uveoscleral outflow.[8,9] In long-term studies, latanoprost 0.005% applied once daily

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reduced intraocular pressure at least as effectively as the β-adrenergic receptor antagonist timolol in patients with primary open-angle glaucoma or ocular hypertension.[6,7]

Unoprostone isopropylate is a docosanoid derived from a metabolite of a primary prostaglandin, 13,14-dihydro-15-ketoprostaglandin. As a prostaglandin compound, it has significant ocular hypotensive effect and was reported to be as effective as timolol in reducing intraocular pressure in primary open-angle glaucoma.[10,11] It is thought to act by increasing uveoscleral outflow, similar to latanoprost.[12,13] However, a study by Taniguchi and associates[14] suggested that unoprostone may increase conventional trabecular outflow.

There is little published literature on the comparison of latanoprost with unoprostone for treatment of primary open-angle glaucoma and ocular hypertension. A comparative study done in glaucomatous monkey eyes showed that latanoprost was more effective than unoprostone in lowering intraocular pressure after 5 days of treatment.[15] The comparison between these two prostaglandin analogues has importance in establishing future guidelines for glaucoma therapy. This is especially so for patients who are intolerant or have contraindications to older glaucoma medications, such as β blockers. There is a need to know if both drugs are interchangeable and if there are individuals who respond to one drug but not the other. It would also be useful to determine drug effectiveness and side effects in individual patients, and their relative response in them. This study was thus done to compare the efficacy of the two drugs with regard to intraocular pressure–reducing effect and side effects in patients with primary open-angle glaucoma and ocular hypertension.

METHODS

THIS TWO-CENTER STUDY WAS CARRIED OUT AT THE TAN Tock Seng Hospital and the National University Hospital, Singapore, and was designed as a randomized double-masked crossover comparison of latanoprost treatment to unoprostone treatment in patients with primary open-angle glaucoma and ocular hypertension. There were two treatment periods of 1 month separated by a 3-week washout period. After obtaining approval from the ethics committees of each center and by the Ministry of Health of Singapore, a signed informed consent was obtained from all patients before study enrollment. The study was performed according to the Declaration of Helsinki and the Singapore guidelines on "Good Clinical Practice."

Patients 40 years of age or older with unilateral or bilateral primary open-angle glaucoma or ocular hypertension were eligible. All patients recruited had intraocular pressure greater than 21 mm Hg at prestudy visit for untreated patients, or intraocular pressure greater than 21 mm Hg at baseline visit after washout of previous monotherapy. Primary open-angle glaucoma was defined as glaucomatous optic neuropathy with a compatible visual field defect and normal angles on gonioscopy, whereas ocular hypertension was defined as normal optic disks, normal visual fields, and open angles on gonioscopy. Glaucomatous optic neuropathy was defined as a cup-to-disk ratio of 0.5 or greater, or the presence of notching. A threshold examination of the central 24 degrees of visual field (program 24 to 2, model 750; Humphrey Instruments, San Leandro, California) showing a glaucoma hemifield test "outside normal limits," and a cluster of three contiguous points on the pattern deviation plot depressed at *P* less than .5% level (of occurring in age-matched normal subjects) not crossing the horizontal meridian, were considered compatible with glaucoma.

Patients on previous glaucoma monotherapy were required to complete a minimum washout period before randomization: 3 weeks for β-adrenergic antagonists, 2 weeks for adrenergic agonists, 5 days for cholinergic agonists, and 5 days for carbonic anhydrase inhibitors. Patients requiring bilateral treatment had to fulfill all eligibility criteria for both eyes to be included. However, if only one eye fulfilled the inclusion criteria, that eye was included as the study eye and the fellow eye could be treated with allocated study therapy provided that no exclusion criteria were met.

Exclusion criteria were gonioscopic appearance of angle closure; secondary glaucoma, such as uveitic, neovascular, or posttrauma; previous intraocular surgery; previous trauma to the eye with damage of the anterior chamber angle; advanced glaucoma (defined as cup-to-disk ratio 0.9 or greater and/or perimetric evidence of visual field loss within 10 degrees of macula fixation in one or more quadrants) at risk for progression during the washout period; the fellow eye on treatment with another intraocular pressure–reducing drug; previous treatment with latanoprost or unoprostone; previous corneal infection or corneal abnormalities; uveitis or dry eyes; current use of contact lenses; oral drugs known to affect intraocular pressure; or known allergy to benzalkonium chloride. Also, a history of cerebrovascular, hepatic, or metabolic disease (except diabetes mellitus) was considered reason for exclusion. Currently pregnant or nursing women or women considering pregnancy were also excluded, as well as patients with a history of noncompliance or patients who participated in another therapeutic drug study within 1 month.

The schedule of examinations and procedures is presented in Table 1. At the prestudy visit, medical and ocular history was taken. Visual acuity and refraction, slit-lamp examination, ophthalmoscopy and measurement of intraocular pressure were performed. Gonioscopy and perimetry were also carried out. This visit took place within 3 weeks before the study start, and the patients were included after these eligibility assessments. Those on monotherapy were washed off the medication. On the baseline day, the patients were randomized to two parallel study

TABLE 1. List of Schedules and Procedures in Each Study Period

Examination	Pre-study	Day 0, Visit 1		Day 2, Visit 2	Day 14, Visit 3	Day 28, Visit 4	
		9 AM	5 PM	9 AM	9 AM	9 AM	5 PM
History	X						
Gonioscopy	X						
Visual field	X						
Ophthalmoscopy	X					X	
Adverse event check	X	X	X	X	X	X	X
Visual acuity	X	X		X	X	X	
Refraction	X						
Slit-lamp examination	X	X	X	X	X	X	X
Intraocular pressure measurement	X	X	X	X	X	X	X
Iris photo	X					X	
Blood pressure	X	X		X	X	X	
Pulse	X	X		X	X	X	

groups: one group was assigned to treatment with placebo in the morning and latanoprost 0.005% in the evening, and the other group received unoprostone 0.12% twice daily, for a duration of 4 weeks. All types of medication were dispensed in identical bottles labeled as "morning" and "evening."

After the first study period, all patients were required to complete a washout period of 3 weeks before being crossed over to the other study medication. Patients then underwent exactly the same regimen of examination and clinic visits as in treatment period 1. During each study period, there were four scheduled visits; at baseline, after 2 days, 14 days, and 28 days.

Intraocular pressure was measured with a Goldmann applanation tonometer. Three measurements were performed in each eye, and the mean of the three measurements was used in the statistical analyses. Intraocular pressure was measured at 9 AM and 5 PM on the baseline and day 28 visits, and at 9 AM on day 2 and day 14 visits of each treatment period. Best-corrected Snellen visual acuity and refractive error, systemic blood pressure, and pulse rate were determined at each visit, and a slit-lamp examination was performed. The presence of cells and flare in the anterior chamber was investigated during slit-lamp examination. Flare was graded as none, moderate, or severe, and cells present in a slit of 2 mm width were graded as none (1 to 2 cells), mild (3 to 5 cells), moderate (6 to 20 cells), or severe (20 cells or more). At the baseline visit, 28-day visit, and last visit, iris photographs were taken and ophthalmoscopy was carried out. Iris photographs were compared and judged on whether there was any change in iris pigmentation.

Patients were instructed to instill one drop of the allocated medication at approximately 8 AM and 8 PM each day. On visit days to the clinic (day 2, day 14, and 28), the eye drops were administered in the mornings at 7 AM before the clinic visit. The 9 AM measurement was thus taken 2 hours and 13 hours after the last drop of unoprostone and latanoprost, and the 5 PM measurement was at 10 and 21 hours, respectively. Patients were informed to adhere strictly to the timing of the last two drops before the clinic visit and recorded the time of administration for verification. The first eye application was at 8 PM on day 0 (the baseline day) and the last application was at 7 AM on day 28 (the last visit) of each study period.

Adverse events were monitored carefully throughout the study. Patients were queried at each visit regarding adverse events by standard clinician enquiry, and investigators did not ask specifically about any particular symptom. An adverse event was defined as any undesirable event occurring in a subject regardless if it was considered related to the investigational drug. A serious adverse event was defined as an event that was potentially fatal, life threatening, permanently disabling, requiring hospitalization, or requiring intervention to prevent permanent impairment or damage.

The trial size was 60 patients. Of these, 30 were randomized to unoprostone in treatment period 1 followed by latanoprost in treatment period 2, and 30 were randomized to latanoprost followed by unoprostone in a crossover design. The trial size was calculated to detect a difference in intraocular pressure between the two treatments of 2.0 mm as determined at week 4 of each treatment period, with a two-sided test size of 5% and power 90%.[16] The between treatment groups SD was estimated to be 3 mm Hg.

For each patient, the intraocular pressure value was calculated at baseline and day 28 of each period as the average of all measurements made on the study eye(s) on that day. If the patient had only one study eye, the average was based on the measurements made in that eye only. For patients in whom both eyes were eligible, the average was based on the measurements made in both eyes. In the event that the patient was missing one or more measurements, the average was based on the nonmissing measurements.

The primary outcome measures were change in intraocular pressure from the start of each period to the end of the period, and percent change in intraocular pressure during each period. Responders were also classified into patients who experienced a percent decrease in intraocular pressure of a fixed level (15% to 30%).

A comparison of the baseline values for treatment period 2 was made to those for treatment period 1. The purpose of this comparison is to detect changes that might be attributable to treatment carryover from period 1, change in disease status, differences in the two groups, or a treatment by period interaction. SAS PROC MIXED version 6.12 (SAS Institute, Inc, Cary, North Carolina) was used to conduct an analysis of covariance: the model used change in intraocular pressure for both periods as

TABLE 2. Baseline Demographic Characteristics of Study Groups

Characteristics	Unoprostone–Latanoprost	Latanoprost–Unoprostone	*P* Value
Number of patients	29	27	
Age (mean ± SD)	64.9 ± 9.9	60.7 ± 10.7	
Maximum	80	86	.24
Minimum	43	45	
Sex			
Male	19	15	.45
Female	10	12	
Race			
Chinese	20	18	
Malay	5	3	.65
Indian	4	5	
Others	—	1	

response, treatment and period as fixed effect factors, baseline intraocular pressure as a covariate, and patient (with sequence of treatment nested) as a random effect.

All statistical tests were conducted using Statistical Package for Social Sciences version 8.0 (SPSS, Inc, Chicago, Illinois).

RESULTS

OF THE 60 PATIENTS RANDOMIZED TO THE STUDY, 56 PAtients (29 unoprostone-latanoprost and 27 latanoprost-unoprostone) completed both treatment periods and had intraocular pressure data available for evaluation. One subject violated the inclusion/exclusion criteria and was excluded. Two patients did not complete the study: one discontinued after study day 2 of the first period because of severe swelling of the eyelids (while on latanoprost), whereas the other defaulted after study day 14 of the first period (because of work commitments). The last subject was found to have intraocular pressure greater than 30 mm Hg during the washout period between the study periods and had timolol added to his therapy (for safety reasons), thus excluding him from the analysis.

Table 2 refers to the baseline demographic characteristics. All patients were Asian (predominantly Chinese), and all eyes had brown irises. The two treatment sequence groups appeared to be balanced at baseline with respect to sex, race, and age. They were comparable with respect to laterality of eyes involved, as well as the type of glaucoma (Table 3). There were 13 subjects who were on previous glaucoma monotherapy and were washed off medication before randomization (Table 4). Other factors, such as medical history, use of concomitant treatment, ocular and systemic symptoms, ocular findings, iris color, and vital signs at the prestudy visit, in the two treatment groups were also similar.

TABLE 3. Diagnosis and Laterality of Affected Eye

	Unoprostone–Latanoprost (n = 29)	Latanoprost–Unoprostone (n = 27)	*P* Value
Type of glaucoma			
Primary open-angle	22	14	.06
Ocular hypertension	7	13	
Laterality			
Right	8	12	.22
Left	8	3	
Bilateral	13	12	

TABLE 4. Patients on Previous Glaucoma Monotherapy

Previous Medication	Unoprostone–Latanoprost (n = 29)	Latanoprost–Unoprostone (n = 27)
Timolol	3	8
Betaxolol	1	0
Dorzolamide	1	0

Table 5 summarizes the intraocular pressure values and changes for both periods

At the start of period 1, the mean baseline intraocular pressure was 24.3 ± 0.6 mm Hg in the unoprostone-treated group and 22.8 ± 0.4 mm Hg in the latanoprost-treated group ($P = .06$).

At the end of period 1, the mean intraocular pressure was 18.5 ± 0.6 mm Hg in the unoprostone-treated group and 17.0 ± 0.5 mm Hg in the latanoprost-treated group. For both treatment groups, the decrease from baseline was statistically significant ($P < .0001$). The mean decrease in intraocular pressure during period 1 was 5.7 ± 0.5 mm Hg for unoprostone-treated patients and 5.8 ± 0.6 mm Hg for latanoprost-treated patients.

The mean difference in intraocular pressure decrease between the two groups was 0.04 mm Hg in favor of latanoprost ($P = .96$). Adjusting for age and mean prestudy intraocular pressure increased the difference to 0.32 mm Hg ($P = .69$).

At the start of period 2, the mean baseline intraocular pressure was 22.2 ± 0.6 mm Hg in the latanoprost-treated group and 20.9 ± 0.5 mm Hg in the unoprostone-treated group ($P = .097$).

At the end of period 2, the mean intraocular pressure was 15.8 ± 0.5 mm Hg in the latanoprost-treated group and 18.4 ± 0.5 mm Hg in the unoprostone-treated group ($P = .001$). The mean decrease in intraocular pressure during period 2 was 6.3 ± 0.6 mm Hg for latanoprost-treated patients and 2.5 ± 0.5 mm Hg for unoprostone-treated patients ($P < .001$). For both treatment groups, the decrease from baseline was statistically significant ($P < .001$).

TABLE 5. Summary of Intraocular Pressure Changes

	Treatment Period 1			Treatment Period 2		
	Start	End	Change	Start	End	Change
Unoprostone treated	24.3 ± 0.6	18.5 ± 0.6	5.7 ± 0.5	20.9 ± 0.5	18.4 ± 0.5	2.5 ± 0.5
Latanoprost treated	22.8 ± 0.4	17.0 ± 0.5	5.8 ± 0.6	22.2 ± 0.6	15.8 ± 0.5	6.3 ± 0.6
P value	.06	.06	.96	.097	.001	<.001

Values are mean ± SEM, in mm Hg.

The mean difference in intraocular pressure decrease between the two groups was 3.8 mm Hg ($P < .001$) in favor of latanoprost. Adjusting for age and mean prestudy intraocular pressure did not change the difference significantly.

A comparison of the baseline values for period 2 was made to those for period 1. The purpose of this comparison is to detect changes that might be attributable to treatment carryover from period 1, change in disease status, differences in the two groups, or a treatment by period interaction. Unfortunately, in a two-period two-treatment crossover design, all of these effects are liaised with each other. In the event that the period 1 and 2 baseline intraocular pressure values are found to differ, it would be impossible to determine in a statistical manner which effect caused the difference.

Based on a paired *t* test, the overall mean baseline intraocular pressure at period 2 was significantly lower than that at period 1 for both groups (unoprostone-latanoprost, $P < .001$; latanoprost-unoprostone, $P = .002$). The explanation for this cannot be obtained statistically for the reasons outlined above.

On checking the duration of washout periods for both groups, the washout criteria for the patients was fully satisfied with a mean of 21 days and 21.1 days for the unoprostone-latanoprost group and latanoprost-unoprostone group, respectively.

SAS PROC MIXED was used to conduct an analysis of covariance: the model used change in intraocular pressure for both periods as response, treatment and period as fixed effect factors, baseline intraocular pressure as a covariate, and patient (with sequence of treatment nested) as a random effect. The difference between the two treatments was significant ($P < .001$) with a significant overall influence of the baseline intraocular pressure value ($P = .005$). Although there were significant effects for both treatment-by-period interaction ($P = .006$) and period ($P = .006$), the two groups behaved in the same manner with respect to this decrease in baseline values. It was thus possible to obtain unbiased estimates of the treatment effect.

The results of this analysis showed that in the latanoprost group, the intraocular pressure decreased from an adjusted baseline of 22.3 ± 0.5 mm Hg to 16.2 ± 0.5 mm Hg, whereas in the unoprostone group, the intraocular pressure decreased from an adjusted baseline of 23.2 ± 0.4 mm Hg to 19.0 ± 0.4 mm Hg. Overall, latanoprost-treated patients experienced an average decrease in intraocular pressure of 6.1 ± 0.5 mm Hg ($P < .001$), whereas the unoprostone-treated patients experienced an average decrease of 4.2 ± 0.4 mm Hg ($P < .001$). The difference of 1.9 mm Hg between treatments was statistically significant in favor of latanoprost ($P = .003$, ANCOVA). Table 6 shows the adjusted intraocular pressure values.

TABLE 6. Summary of Intraocular Pressure Values After Adjustment

	Adjusted Baseline IOP	Adjusted IOP Reduction
Unoprostone	23.2 ± 0.8	4.2 ± 0.4
Latanoprost	22.3 ± 0.4	6.1 ± 0.5

IOP = intraocular pressure.
Values are mean ± SEM, in mm Hg.

An unadjusted analysis of responders using the percent decrease in intraocular pressure definition is given in Table 7. Overall, the proportion of responders in the latanoprost-treated group is greater than in the unoprostone-treated group. This is true for each of the target cut-points (15% decrease, 20%, 25%, and 30%).

In terms of absolute intraocular pressure change, there were 41 subjects (73.2%) in whom the intraocular pressure reduction of latanoprost was greater. There were 15 subjects (26.8%) in whom the response of unoprostone was greater.

The adverse events experienced by the patients are summarized in Table 8. There were few systemic adverse events, and those present (such as skin rash, headache, and giddiness) were mild in nature. Only one subject in the study stopped the trial medication (in this case latanoprost), because she developed severe eyelid swelling after applying the drops. This resolved on stopping the medication and was likely to be an allergic reaction.

The most common adverse events were ocular irritation and redness. Comparing the two groups, almost twice as many eyes receiving unoprostone experienced ocular irri-

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