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Switching to latanoprost monotherapy for 24 weeks in glaucoma patients

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PURPOSE. *To investigate the intraocular pressure lowering effect in glaucoma patients switched to latanoprost therapy from isopropyl unoprostone given as monotherapy or in combination with a β-blocker.*

METHODS. *Patients with primary open angle glaucoma or normal tension glaucoma treated with 0.12% isopropyl unoprostone as monotherapy or in combination with a β-blocker were eligible for this single-center clinical study. Of the 51 patients (51 eyes) enrolled, 18 were men and 33 were women aged 62.1 ± 12.3 years (mean ± SD). Twenty-two patients had primary open angle glaucoma, and 29 patients had normal tension glaucoma. Intraocular pressure was measured twice within 3 months prior to the switch, and the mean value was taken as the baseline. The patients were then switched to latanoprost (0.005%) monotherapy (once-daily administration), and changes in intraocular pressure were monitored. One physician measured intraocular pressure after 4, 8, 16, and 24 weeks of administration in this 24-week study.*

RESULTS. *The mean intraocular pressures were 16.0 ± 2.4 mmHg at baseline, 13.7 ± 2.3 mmHg after 4 weeks, 13.1 ± 2.1 mmHg after 8 weeks, 13.6 ± 2.0 mmHg after 16 weeks, and 13.3 ± 2.4 mmHg after 24 weeks. A significant decrease in intraocular pressure was noted at all time points in both groups (paired t-test, $p<0.0001$), and the intraocular pressure lowering effect persisted through week 24 of administration (analysis of variance, $p<0.0001$).*

CONCLUSIONS. *Switching to latanoprost monotherapy elicits further reduction in intraocular pressure in patients with primary open angle glaucoma or normal tension glaucoma. (Eur J Ophthalmol 2004; 14: 401-6)*

KEY WORDS. *β-antagonist, Intraocular pressure, Latanoprost, Monotherapy, Unoprostone*

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INTRODUCTION

Latanoprost, a prostaglandin $F_{2\alpha}$ derivative, is a drug used in the treatment of glaucoma that decreases intraocular pressure (IOP) by increasing the uveoscleral outflow (1-4). It became available on the market in Japan in May 1999. Isopropyl unoprostone is a prostaglandin metabolite that was developed in Japan and became available in October 1994, prior to latanoprost. It has been approved for all types of glaucoma and intraocular hypertension and is used on a twice-daily administration schedule. It was initially thought to lower IOP through a mechanism similar to latanoprost (5, 6), but its mechanism of action

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is unclear. It has been suggested that it may lower IOP via the conventional route (7). Few reports have directly compared the intraocular hypotensive effect of these drugs (8, 9). It may be possible to improve compliance if good IOP control is achieved with latanoprost, which requires less frequent ophthalmic administration than isopropyl unoprostone. We conducted a prospective study of the intraocular hypotensive effect in patients with primary open angle glaucoma (POAG) or normal tension glaucoma (NTG) who were previously treated with unoprostone as monotherapy or in combination with a β-blocker and then switched to latanoprost monotherapy.

SUBJECTS AND METHODS

A 24-week single-center clinical study was conducted in 51 patients (51 eyes) presenting to the glaucoma outpatient clinic of this department from August 1, 2000, to January 31, 2001, with POAG or NTG who were being treated with 0.12% isopropyl unoprostone as monotherapy or in combination with a β-blocker on a twice-daily administration schedule (Tab. I). In order to eliminate any arbitrary factors from patient selection, all of the patients in this clinic meeting the above criteria during the period were asked to participate in the study, and informed consent was obtained from all patients enrolled. There were 18 men and 33 women aged 62.1±12.3 years (mean ± SD). Twenty-two patients had POAG, and 29 patients had NTG. At the time of switching the drug regimen, the mean spherical equivalent refraction was -0.94±3.11 D, and the mean deviation (MD) measured using the Humphrey Field Analyzer (central 30-2 program) was -3.11±4.12 dB. Prior to switching, 17 eyes in 17 subjects were being treated with isopropyl unoprostone (Group A), and 34 eyes in 34 patients were being treated with isopropyl unoprostone and a β-blocker (Group B). In Group B, the β-blockers used were timolol (0.5%) in 15 subjects, 2% carteolol in 10 subjects, betaxolol in 8 subjects, and Nipradilol in 1 subject.

Patients with a history of previous ocular surgery, uveitis, or previous laser treatment and contact lens users were excluded from this study.

In all patients, IOP was measured twice on two different days (separated by an interval of 4 weeks or longer) between 9:30 am and 12:30 pm within 3 months prior to switching to latanoprost. The mean value was taken as the baseline IOP. All of the patients were switched to latanoprost monotherapy without washing out the previous medication. Latanoprost was instilled once daily at 9:00 pm. The patients were instructed to wipe off any excess eye drop solution around their eyes and to wash their faces after instillation. The patients were seen at the outpatient clinic at the same time as before the switch, and the same physician measured IOP using the same slit lamp biomicroscope. IOP was measured at 4, 8, 16, and 24 weeks after switching, and on each observation day, local ocular conditions were observed under the slit lamp biomicroscope. Furthermore, patients were interviewed for the presence/absence of subjective symptoms including systemic symptoms. A Goldmann applanation tonometer was used to measure IOP in all patients.

To determine the changes in IOP in each patient, one eye was selected for the measurements in each patient. If therapy switching to latanoprost involved only one eye, the value of the eye selected was followed. If the therapy was switched to latanoprost in both eyes, the eye with the higher baseline was followed. The right eye was followed if both eyes had the same baseline value.

For statistical analysis, analysis of variance (ANOVA) or the t-test was used depending on the variables evaluated. A two-sided level of $p<0.05$ was considered significant.

TABLE I - PATIENTS PROFILE

	Group A	Group B	Total
No. of cases	17	34	51
Age (mean ± SD)	62.8±12.9	61.6±12.3	62.1±12.3
Gender			
Male	5	13	18
Female	12	21	33
Type			
POAG	3	19	22
NTG	4	15	29
Diopter (mean ± SD)	-1.11±3.13	-1.49±3.28	-1.34±3.23
Humphrey (mean ± SD)	-3.15±4.30	-2.20±3.79	-3.11±4.12

Group A: Isopropyl unoprostone monotherapy prior to latanoprost
Group B: Combination therapy with isopropyl unoprostone and β-blocker prior to latanoprost

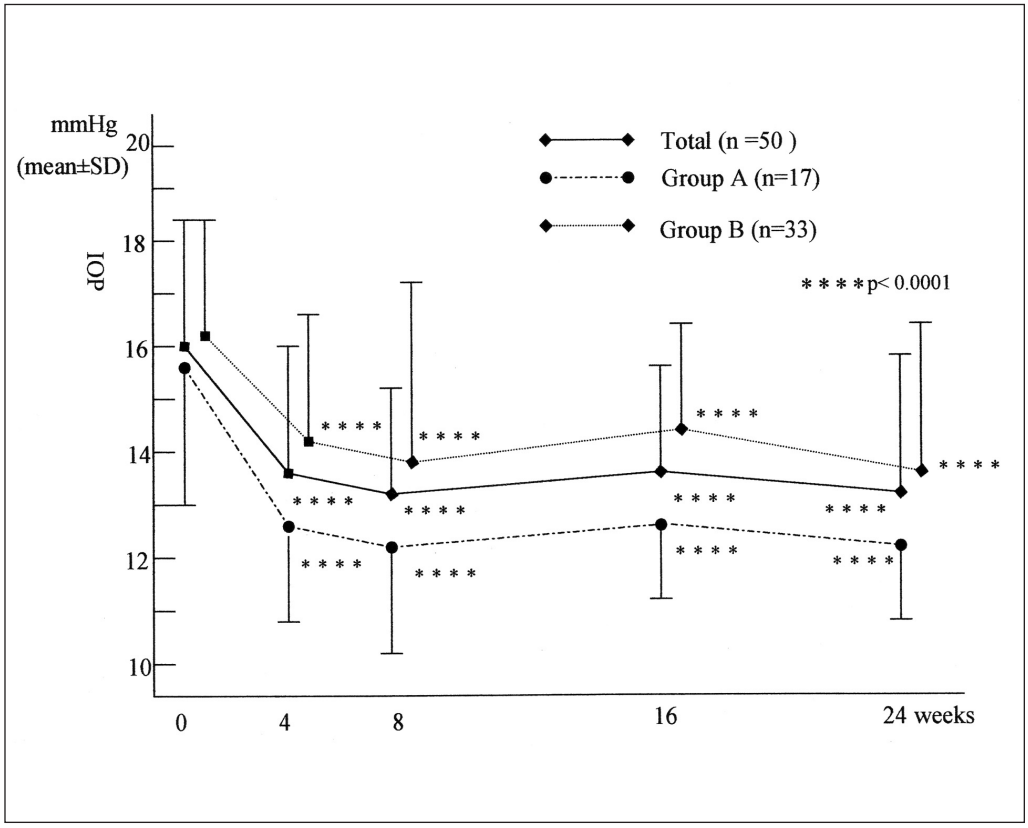

Fig. 1 - *Group A: Patients on isopropyl unoprostone monotherapy prior to latanoprost. Group B: Patients on combination therapy with isopropyl unoprostone and a β-blocker prior to latanoprost. Statistical analysis: Comparison between baseline value and the value at each time point, paired t-test. Intraocular pressure value: mean ± standard deviation.*

RESULTS

One patient in Group B complained of a dull headache in the occipital region 10 days after switching, and instillation of latanoprost was discontinued in this patient. Accordingly, 50 patients were available for analysis of IOP. The treatment regimen was not altered in any of the patients, nor was another treatment regimen added because of a rise in IOP during the study period.

The IOP in 50 patients changed from 16.0±2.4 mmHg (mean ± SD) at baseline to 13.7±2.3 mmHg after 4 weeks, 13.1±2.1 mmHg after 8 weeks, 13.6±2.0 mmHg after 16 weeks, and 13.3±2.4 mmHg after 24 weeks. Because a significant change was noted in ANOVA using the time point as a variable, the differ-

TABLE II - INTRAOCULAR PRESSURE REDUCTION

		4 Week	8 Week	16 Week	24 Week
Group A	ΔIOP	2.9±1.7	3.2±1.9	3.0±1.9	3.3±1.8
(17 cases)	(%)*	(18.3±8.5)	(19.9±10.2)	(17.0±9.9)	(20.1±8.7)
Group B	ΔIOP	2.1±1.5	2.7±1.5	2.2±1.5	2.3±1.9
(33 cases)	(%)*	(12.6±9.0)	(16.2±8.7)	(12.1±8.4)	(14.3±11.4)

Intraocular pressure reduction (ΔIOP): Baseline intraocular pressure value - Intraocular pressure value at each time point after switching

(%)* = Intraocular pressure reduction rate

$$\frac{\text{Baseline intraocular pressure value - Intraocular pressure value at each time point after switching}}{\text{Baseline intraocular pressure value}} \times 100$$

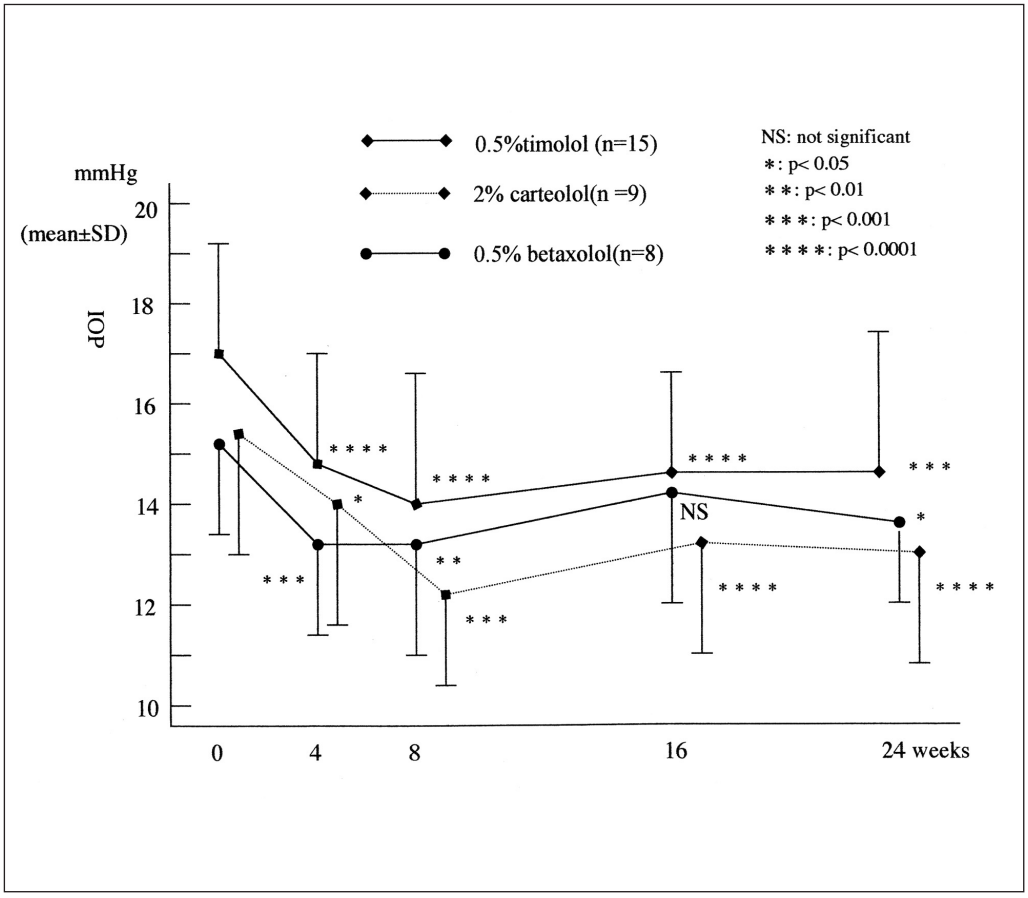

Fig. 2 - ◆—◆ *The β-blocker used concomitantly before switching to latanoprost was 0.5% timolol maleate.* ◆·····◆ *The β-blocker used concomitantly before switching to latanoprost was 2% carteolol hydrochloride.* ●—● *The β-blocker used concomitantly before switching to latanoprost was betaxolol hydrochloride. Statistical analysis: Comparison between baseline value and the value at each time point, paired t-test. Intraocular pressure value: mean ± standard deviation.*

ence between the week 0 value and the value at each time point was studied using the paired t-test ($p<0.0001$). A significant fall was noted at each time point, and the IOP-lowering effect persisted to week 24 of administration (ANOVA, $p<0.0001$) (Fig. 1).

In Group A (17 subjects), the IOP was 15.6±2.6 mmHg at baseline and 12.4±1.7 mmHg at 24 weeks, while in Group B (33 subjects), IOP was 16.2±2.3 mmHg at baseline and 13.8±2.5 mmHg at 24 weeks.

When Group A and Group B were analyzed separately, a statistically significant fall in IOP was observed at each time point, and the IOP-lowering effect was observed for 24 weeks to the same degree in both groups (ANOVA, $p<0.0001$).

In Group A, IOP was reduced by 2.9±1.7 mmHg after 4 weeks ($p<0.0001$) (IOP reduction rate: 18.3 ± 8.5%), and in Group B, IOP was reduced by 2.1±1.5 mmHg after 4 weeks ($p<0.0001$) (IOP reduction rate: 12.6 ± 9.0%) (Fig. 2).

When Group B was stratified based on the type of β-blocker used with unoprostone prior to switching, all subgroups showed a significant decrease in IOP at all time points in the paired t-test, except for betaxolol at week 16 after the switch. The effect persisted for the duration of the study (Fig. 2).

Nipradilol was excluded from the analysis because the number of patients who had used it was small.

Adverse reactions to the instillation of latanoprost are shown in Table III. Including overlaps, adverse reactions were noted in 16 patients (31.4%), including hyperpigmentation of the iris in 2 patients (3.9%), hyperpigmentation of the eyelid in 6 patients (11.8%), and hypertrichosis of the eyelid (including the eyelashes) in 8 patients (15.7%). All symptoms appeared between week 8 and week 24, but latanoprost instillation was continued. In one patient who experienced a dull headache in the occipital region 10 days after switching, instillation of latanoprost was discontin-

TABLE III - ADVERSE DRUG REACTIONS

1. Cases in which instillation was continued (including overlaps)		
		Time until onset of symptom
Hyperpigmentation of the iris	2 cases (3.9%)	14.0 weeks
Hyperpigmentation of the eyelid	6 cases (11.8%)	11.3±3.0 weeks
Hypertrichosis of the eyelid	8 cases (15.7%)	14.2±4.9 weeks
2. Cases in which instillation was discontinued (dropouts)		
Dull headache	1 case (2.0%)	10 days

ued at the patient's request. The local ocular symptoms described above appeared in both eyes in the patients who received instillation of latanoprost in both eyes. In one patient who concurrently experienced hyperpigmentation of the iris and hypertrichosis of the eyelid, the same symptoms had already been noted on instillation of isopropyl unoprostone, and the patient reported the subjective impression that the symptoms were exacerbated after switching to latanoprost.

None of the patients experienced any adverse effects on the corneal epithelium or any systemic effects.

DISCUSSION

It has been reported that latanoprost exerts a more potent IOP-lowering effect than timolol maleate when administered to glaucoma patients (1, 3). On the other hand, it has been reported that the IOP-lowering effect of isopropyl unoprostone is weaker than that of timolol maleate and comparable to that of betaxolol hydrochloride (10). Furthermore, some researchers have reported that Xalatan exhibits a more potent IOP-lowering effect than isopropyl unoprostone (8, 9). It has also been reported that when patients are switched from timolol maleate to latanoprost, a further reduction in IOP can be achieved (11).

In the current study, when the patients were switched from combination therapy with isopropyl unoprostone and a β-blocker to Xalatan monotherapy, a significant fall in IOP was maintained during the 24-week observation period, suggesting that Xalatan has a potent IOP-lowering effect and that the effect is stable and persistent.

The adverse reactions to instillation of latanoprost, hyperpigmentation of the iris (4, 11-13), hyperpigmentation of the eyelid, and hypertrichosis around the eye, have previously been reported (12-14). In this study, therefore, the patients were instructed to wipe off any excess liquid around their eyes and wash their faces after instillation of latanoprost, but the above reactions were nevertheless noted in 14 patients (27.5%, including the overlaps). None of the patients who experienced these symptoms asked to discontinue the instillation of latanoprost, but from a cosmetic viewpoint, it is necessary to lower the incidence of these effects.

Similar adverse reactions have also been reported in patients treated with isopropyl unoprostone (14), but in this study, only one patient experienced hyperpigmentation of the iris and hypertrichosis of the eyelid with the previous isopropyl unoprostone monotherapy; this patient reported that the subjective symptoms were exacerbated after switching to latanoprost. In the other patients, the above adverse reactions did not appear until the instillation of latanoprost was started, suggesting that latanoprost may induce these adverse reactions more strongly and more frequently than isopropyl unoprostone.

In the one patient in whom instillation of latanoprost was discontinued due to a dull headache in the occipital region, the etiology of the headache was unclear, but because the symptom disappeared immediately after discontinuation of instillation, a causal relation with instillation of latanoprost is likely.

In conclusion, this study shows that when patients

are switched from isopropyl unoprostone monotherapy or combination therapy with isopropyl unoprostone and a β-blocker to latanoprost monotherapy, further decreases in IOP can be achieved and maintained, and that switching to latanoprost is suitable for glaucoma patients who are already on treatment.

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