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Prognostic Factors for Hypotensive Effects of Isopropyl Unoprostone in Eyes With Primary Open-Angle Glaucoma

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Abstract: It has been reported that isopropyl unoprostone, a prostaglandin-related compound, has potent effects in lowering intraocular pressure and that its hypotensive effect is an increase of uveoscleral outflow. In the present study, we investigated the clinical characteristics of the hypotensive effects of this novel antiglaucoma drug in 115 primary open-angle glaucoma (POAG) eyes. The mean intraocular pressure (± standard deviation) before the addition of isopropyl unoprostone to the current regimens was 21.3 ± 4.4 mmHg. The values at 1 month, 3 months, and 6 months after treatment were, respectively, 20.2 ± 3.9 mmHg, 19.4 ± 3.4 mmHg, and 18.4 ± 2.5 mmHg. In POAG, the outflow pressure difference (ΔOP), which is determined as (pretreatment pressure − posttreatment pressure)/(pretreatment pressure −10) × 100 (%), was reduced by more than 20% in 36 (31%) of 115 eyes, 35 (36%) of 97 eyes, and 33 (53%) of 62 eyes, respectively at 1, 3, and 6 months. We defined the "early success" group as eyes with a significant reduction in ΔOP (≥20%) at 1-month posttreatment. To identify the prognostic factors related to the significant reduction in intraocular pressure occurring after the administration of this drug, we carried out a statistical analysis by logistic regression analysis. Statistical analysis revealed significant prognostic factors: history of cataract surgery ($P = 0.0084$) and pretreatment pressure levels ($P = 0.0105$) at 1-month posttreatment. Also, further statistical analysis showed a significant influence of pretreatment pressure levels ($P = 0.0010$) at 3 months posttreatment. Our study shows an interindividual difference in the responsiveness of hypotensive effects on POAG eyes and some prognostic factors (history of cataract surgery and pretreatment pressure levels) prior to the use of this drug. **Jpn J Ophthalmol 1998;42:417–423** © 1998 Japanese Ophthalmological Society

Key Words: Intraocular pressure lowering effects, isopropyl unoprostone, primary open-angle glaucoma, prostaglandin-related compound.

Introduction

The present antiglaucoma medication includes adrenergic agonists and β antagonists, cholinergic agonists, carbonic anhydrase inhibitors, and hyperosmotic agents. Recently, prostaglandins and their related compounds have been intensively investigated in an effort to develop novel antiglaucoma medication because prostaglandin $F_{2\alpha}$ and its derivatives have been shown to significantly lower intraocular pressure.[1–3] Isopropyl 20-ethyl-9-α, 11α-dihydroxy-15-keto-cis-Δ^5-prostonate (isopropyl unoprostone), a prostaglandin $F_{2\alpha}$-related compound, has been developed as a novel intraocular pressure lowering drug.[4,5] As shown in the hypotensive effects of prostaglandin $F_{2\alpha}$[6,7] this compound is also effective in lowering intraocular pressure levels with a different mechanism than other currently available antiglaucoma medication.[8] In the present study, we will report the hypotensive effects of this drug in eyes with primary open-angle glaucoma (POAG), and show that the pretreatment intraocular pressure levels and the history of cataract surgery are prognostic factors for the responsiveness of eyes to the addition of this drug to the current regimens.

Patients and Methods

Included in this study were 64 POAG patients (115 eyes), who had been treated with isopropyl

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unoprostone in the Glaucoma Clinic at Kyoto University Hospital. Follow-up periods were at least 1 month. During the follow-up periods, eyes in which another antiglaucoma medication was administered, or the medication regimen changed, or for which surgical treatment was required to treat uncontrolled intraocular pressure, were excluded from this study. The patients included 35 men and 29 women, and the mean age (± standard deviation) of the patients was 62.5 ± 15.0 years. In 15 eyes (10 patients) cataract surgery had been performed prior to entry in this study. In 13 eyes (9 patients) of these 15 eyes, an intraocular lens had been implanted. In addition, in 18 eyes of 13 patients, glaucoma surgery had been performed prior to entry in this study. Surgical treatment for glaucoma included trabeculotomy ab externo in 7 eyes, trabeculectomy in 11 eyes, and multiple surgeries in 2 eyes (trabeculotomy twice in one eye, and trabeculectomy twice in one eye). The mean intraocular pressure (± standard deviation) prior to treatment with isopropyl unoprostone was 21.3 ± 4.4 mmHg. The number of antiglaucoma medications used was none in 4 eyes, one in 67 eyes, two in 26 eyes, three in 16 eyes, and four in 2 eyes. The average number of antiglaucoma medications was 1.5 ± 1.0 at entry in this study.

Results

Intraocular Pressure and Complications

In the 115 eyes with POAG, the mean intraocular pressure (± standard deviation) at the beginning of this study and at 1 month after the addition of isopropyl unoprostone to the medication regimen was 21.3 ± 4.4 mmHg and 20.2 ± 3.9 mmHg, which are significantly different (paired *t*-test, $P = 0.0004$; Table 1). After the first month of the follow-up period, the use of isopropyl unoprostone was suspended in 18 (16%) of the 115 eyes because surgical treatment was performed in 3 eyes, the administration of other drugs in 7 eyes, and serious discomfort related to the use of isopropyl unoprostone occurred in 7 eyes and drop out in 1 eye (Table 2). Complications caused by the use of isopropyl unoprostone included ocular discomfort in 17 eyes (10%), corneal epithelial damage in 8 eyes (5%), blurred vision in 2 eyes (1%), itching in 2 eyes (1%), and redness in 1 eye (0.6%). Reasons for discontinuing the use of isopropyl unoprostone eyedrops in 8 eyes were ocular discomfort in 5 eyes, blurred vision in 2 eyes, and redness in one eye.

Table 2. Number of Eyes Included in This Study

	Posttreatment (Months)	
	1	3
During follow-up	97	44
Required surgical treatment performed	3	0
Addition of drug	7	5
Serious discomfort	7	1
Drop out	1	47
Total	115	97

In 97 eyes in which the follow-up periods were longer than 3 months, the mean intraocular pressure (± standard deviation) before and 3 months after the addition of isopropyl unoprostone were 20.6 ± 4.0 mmHg and 19.4 ± 3.4 mmHg, which are significantly different (paired *t*-test, $P = 0.0005$). Additionally, in 62 eyes in which the follow-up periods were longer than 6 months, the mean intraocular pressure (± standard deviation) before and 6 months after the addition of isopropyl unoprostone were 20.1 ± 3.5 mmHg and 18.4 ± 2.5 mmHg, which were significantly different (paired *t*-test, $P = 0.0097$; Table 1).

Outflow Pressure

We calculated the outflow pressure difference (ΔOP), which is defined as (pretreatment pressure − posttreatment pressure)/(pretreatment pressure − 10) × 100 (%), and attempted to investigate the relationships between the pretreatment factors and the responsiveness of ΔOP to isopropyl unoprostone. "Early success" was defined as ΔOP equal to or more than 20% 1 month after the addition of isopropyl unoprostone. In 36 (31%) of the 115 POAG eyes

Table 1. Intraocular Pressure (IOP) After Treatment With Isopropyl Unoprostone

		Posttreatment (months)		
	Pretreatment	1	3	6
Mean ± standard deviation	21.3 ± 4.4	20.2 ± 3.9	19.4 ± 3.4	18.4 ± 2.5
Number of eyes	115	115	97	62

Table 3. Outflow Pressure Difference After Treatment with Isopropyl Unoprostone

Ratio	Posttreatment (months) 1	3	6
$< 0\%$	38 (33%)	29 (30%)	18 (29%)
$0\% \leqq < 10\%$	24 (21%)	22 (23%)	6 (10%)
$10\% \leqq < 20\%$	17 (15%)	11 (11%)	5 (8%)
$20\% \leqq < 30\%$	12 (10%)	11 (11%)	13 (21%)
$30\% \leqq$	24 (21%)	24 (25%)	20 (32%)

Outflow pressure difference was calculated as follows: Outflow pressure difference = (IOPpre – IOPpost)/(IOPpre – 10) × 100.

the use of isopropyl unoprostone resulted in an "early success" (Table 3). In the remaining 79 eyes, the use of isopropyl unoprostone resulted in an "early failure." In the 36 eyes of the "early success" group and the 79 eyes of the "early failure" group, respectively, ΔOP was 38.5 ± 15.4% and −13.9 ± 34.2%.

In 29 "early success" eyes and 68 "early failure" eyes with follow-up periods longer than 3 months, we analyzed the changes in ΔOP between the first and the third months. In 19 (66%) of the 29 "early success" eyes intraocular pressure level was regarded as "success" (ΔOP ≥ 20%) at the third posttreatment month. On the other hand, in 16 (24%) of the 68 "early failure" eyes intraocular pressure level was regarded as "success" (ΔOP ≥ 20%) at the third posttreatment month. Statistical analysis shows a significant difference between the "early success" and "early failure" groups ($P = 0.0001$). Thus, it seems that eyes with an "early success" in isopropyl unoprostone treatment at the first posttreatment month are also similarly responsive to this drug even at the third month, which suggests reproducibility in the responsiveness of each patient during the follow-up periods (Table 4).

Table 4. Correlation Between Outflow Pressure Differences at First and Third Posttreatment Months

	Outflow Pressure Difference 3 Months	
	Success	Failure
Early success (1 month) ($n = 29$)	19	10
Early failure (1 month) ($n = 68$)	16	52

$P < 0.0001$, chi-square test.

Statistical Analysis

In an attempt to elucidate the prognostic pretreatment factors related to the hypotensive effects of isopropyl unoprostone, we carried out a statistical analysis, with the use of logistic procedures in the SAS system, on the 115 POAG eyes. For the analysis, we had obtained clinical data on gender, age, history of cataract surgery, history of glaucoma surgery, previous medical treatment, and pretreatment for intraocular pressure. "Early success" was defined as described above (ΔOP ≥ 20%) at the first posttreatment month.

First, we calculated Spearman correlation coefficients for relationships between dependent variables ("early success") and independent factors (β-antagonists, pilocarpine, dipivefrin hydrochloride [DPE], acetazolamide, gender, age, history of glaucoma surgery, history of cataract surgery, and pretreatment intraocular pressure). Significant correlations were shown from the Spearman correlation coefficients between "success" and the use of DPE ($P = 0.0406$), history of cataract surgery ($P = 0.0099$), and pretreatment intraocular pressure ($P = 0.0019$). Moreover, in an attempt to elucidate interactions between the antiglaucoma medication already used and the addition of isopropyl unoprostone, we carried out a single variable analysis using logistic regression. The closest relationship was found between "success" and DPE, although the difference was not statistically significant ($P = 0.0516$, Fisher's exact test). Interactions between "success" and the use of other drugs were not significant (Table 5).

Next, we selected independent factors for logistic regression analysis with the use of stepwise, forward selection, and backward elimination procedures. All three procedures showed that, among the selected

Table 5. Statistical Analysis by Fisher's Test

Factor	Outflow Pressure Difference (P Values[a]) 1 month	3 months
Age	0.135	0.792
IOPpre	0.0069*	< 0.0001*
β-blocker	1.000	0.303
Pilocarpine	0.840	0.208
DPE	0.0516	0.258
CAI	1.000	1.000
Gender	1.000	0.054
Glaucoma surgery	1.000	1.000
Cataract surgery	0.016*	0.718

CAI = carbonic anhydrase inhibitor; DPE = dipivefrin hydrochloride; IOP = introcular pressure.
[a]P values are calculated by Fisher's test.
*Statistically significant.

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Table 6. Logistic Regression Analysis Using Chosen Dependent Factors

	Outflow Pressure Difference			
	1 month		3 months	
	P Values	Odds Ratio	*P* Values	Odds Ratio
Cataract surgery	0.0084*	5.51	0.3796	2.14
Pretreatment IOP	0.0105*	4.80	0.0010*	0.03
Age	0.0539	0.26	0.2531	0.986

IOP = intraocular pressure.
*Statistically significant.

independent factors, pretreatment intraocular pressure, history of cataract surgery, and age appeared to be most closely correlated with "early success." Furthermore, to clearly elucidate the clinical implications, we divided two variables into two categories: age ≤75/age >75; pretreatment IOP ≤ 18 mmHg/ pretreatment IOP >18 mmHg. Thus, with the selected three independent variables, a multivariate analysis using logistic regression was carried out. With "early success" (ΔOP > 20% at one month) as a dependent variable, multivariate analysis using logistic regression showed significant correlations between "early success" and history of cataract surgery ($P = 0.0084$) and pretreatment intraocular pressure ($P = 0.0105$) (Table 6, Figures 1 and 2). In addition, there was a tendency for the age to be associated with the effectiveness of isopropyl unoprostone to lower intraocular pressure ($P = 0.0539$) (Table 6, Figure 3).

Similar statistical analysis of the data at the third posttreatment month was carried out. With the "success" (ΔOP ≥ 20%) at the third posttreatment month as a dependent variable, additional multivariate analysis using logistic regression showed significant correlations between "success" and pretreatment intraocular pressure ($P = 0.0010$), but not for history of cataract surgery ($P = 0.3796$) (Table 6, Figure 4).

Discussion

Prostaglandin $F_{2\alpha}$ and its derivatives have been shown to significantly lower intraocular pressure by a different mechanism than other currently available antiglaucoma medications. Some investigations have suggested that the pressure-lowering effect of prostaglandin-related compounds may be caused by increased uveoscleral aqueous outflow.[6,7] Isopropyl 20-ethyl-9α, 11α-dihydroxy-15-keto-cis-Δ^5-prostonate (isopropyl unoprostone) is a prostaglandin $F_{2\alpha}$-related compound, and its pressure-lowering effects on intraocular pressure have been shown to differ from

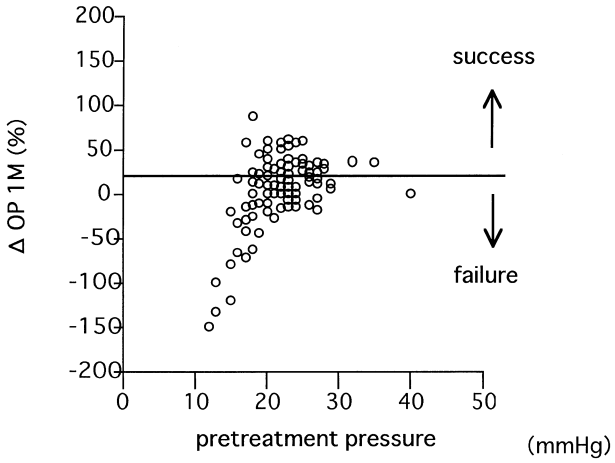

Figure 1. Pretreatment intraocular pressure and outflow pressure difference (ΔOP).

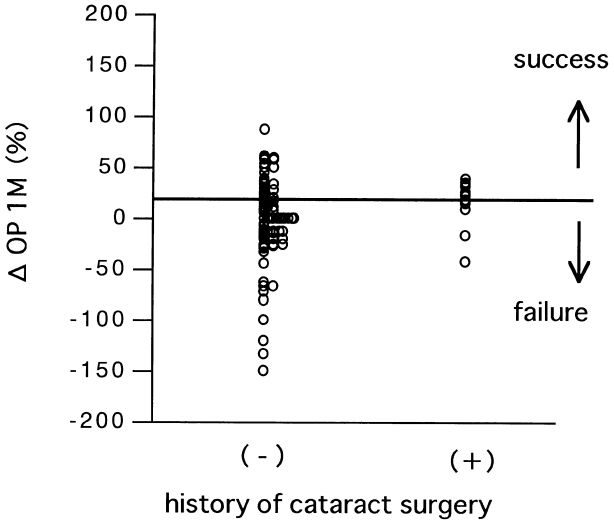

Figure 2. History of cataract surgery and outflow pressure difference.

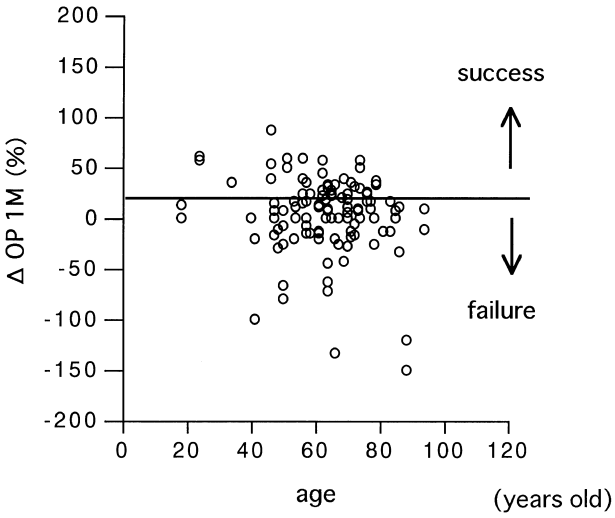

Figure 3. Age and outflow pressure difference.

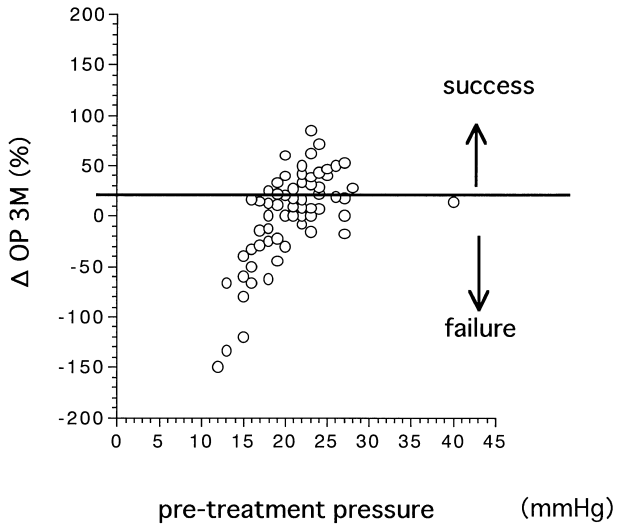

Figure 4. Pretreatment intraocular pressure and outflow pressure difference.

those of currently known antiglaucoma medications. Sakurai et al[8] reported increased aqueous turnover in the anterior chamber and increased pressure-independent aqueous outflow, which suggested that the drug effects may change the outflow to an unconventional outflow route. Accordingly, it is possible that the pressure-lowering effects of this novel drug may have synergistic action with the currently available antiglaucoma medication, even in refractory glaucomatous patients in whom current medical treatment is ineffective. Previous reports indicated that this novel eyedrop is a useful drug for lowering intraocular pressure in glaucoma patients[9–11] as well as in healthy volunteers.[12,13] In this study, a significant decrease in intraocular pressure ("early success"), an outflow pressure difference (ΔOP) >20%, was obtained in 36 (31%) of the 115 POAG eyes after the addition of isopropyl unoprostone. Because the patients included in this study were refractory cases resistant to other medical antiglaucoma treatments, about one third of the proportion of "successful cases" may indicate that this novel drug is useful for lowering intraocular pressure in glaucomatous patients. Indeed, some preliminary reports on the clinical use of isopropyl unoprostone on refractory glaucoma have suggested that this drug may synergistically lower the intraocular pressure with other antiglaucoma medication in eyes that have already been treated with several antiglaucoma medications.[9,10,14] On the other hand, some investigations using animal eyes have suggested that pilocarpine may inhibit the pressure-lowering effects of prostaglandins probably via blockade of the uveoscleral outflow route.[7,15] However, our results did not show any significant inhibition of the hypotensive effects of isopropyl unoprostone on eyes treated with pilocarpine, which appears to agree with previous clinical reports on isopropyl unoprostone.[9,11] However, statistical analysis implies that prior use of DPE may be related to the responsiveness in the hypotensive effects of isopropyl unoprostone, but a statistically significant difference was not shown ($P = 0.0516$, Fisher's exact test). This may be caused by the interaction between the hypotensive effects of DPE and the prostaglandin-related compound, both of which are associated with alteration in the aqueous outflow resistance,[6,7,16,17] although we are unable to explain this exact mechanism at present. Additionally, in the interpretation of the interaction between DPE and isopropyl unoprostone, attention should be paid to the background factors, because this *P* value was calculated from the chi-square test and the retrospective design of the present study introduces limitations to its reliability. Further basic and clinical studies will be required to elucidate the exact interactions between isopropyl unoprostone and other antiglaucoma drugs.

One of the most important points in discussing the clinical application of this novel drug relates to the indications, as there are other medical options for the treatment of open angle glaucoma. Thus, the question to be answered is: in which cases is the use of isopropyl unoprostone the preferred treatment? In this report, we have shown that intraocular pressure prior to the use of isopropyl unoprostone and

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history of cataract surgery may be significant prognostic factors for responsiveness in lowering intraocular pressure. Our results in this retrospective study indicate that, at the first posttreatment month, the use of isopropyl unoprostone is more effective in controlling intraocular pressure in eyes with a history of cataract surgery than in phakic eyes. Furthermore, our "success" rate in eyes with relatively higher preoperative intraocular pressure was somewhat higher than that in eyes with lower preoperative intraocular pressure. Cataract surgery has been reported to influence intraocular pressure levels in several ways. Some investigators have shown that removal of the cataract itself may lower intraocular pressure after surgery, although the intraocular pressure-lowering effects of cataract surgery have been controversial.[18–20] The most likely hypothesis on the association of cataract surgery with responsiveness to the use of isopropyl unoprostone may be alteration in the uveoscleral outflow route. Several basic studies have indicated that the anterior chamber deepening decreases aqueous outflow resistance,[21] hence the presence of the lens may be associated with the aqueous outflow route via the tension of ciliary muscles. In addition, a significant interaction between the pretreatment intraocular pressure level and the use of isopropyl unoprostone may imply the limitation of medically induced effects on lowering intraocular pressure, even with prostaglandin-related compounds. Generally, outflow pressure differences after the addition of a hypotensive drug for the unconventional outflow are lower in eyes with high pressure levels. However, our data showed the tendency that hypotensive effects of isopropyl unoprostone are more effective on eyes with higher pretreatment pressure levels, which appears to be contrary to the above-mentioned general rule. Although we are not able to clarify the mechanism responsible for this contradiction at present; one possible explanation may be the interaction with other hypotensive, antiglaucoma medication. It is difficult for us to completely exclude the influence of other hypotensive drugs because our study included glaucomatous eyes undergoing medical treatment. Also, it may be possible that there are additional effects on the conventional outflow route in addition to hypotensive effects on uveoscleral outflow route, although the present clinical study did not show any evidence for this possibility.

Most aqueous humor driven from the eye is thought to enter the venous system, where the venous pressure level is believed to be around 10 mmHg.[22,23] Thus, although medical modulation of the aqueous outflow with antiglaucoma medication may decrease the resistance in the outflow route, the effects of the medicine in lowering intraocular pressure may be limited by this venous pressure, in addition to the intrinsic resistance in the ocular tissues. Furthermore, although a significant difference was not shown in this study, our results suggested a tendency for medication to be more effective in controlling intraocular pressure in younger and middle-aged glaucomatous cases than in elderly patients, but this relationship could not be seen at 3 months. The aging of ocular tissues may also confer an added influence on the aqueous outflow route in glaucomatous eyes. In glaucomatous eyes of elderly patients, age-dependent changes in the structure and function of the trabecular meshwork and Schlemm's canal have been suggested by several investigators.[24,25] Furthermore, long-standing use of antiglaucoma medication, such as pilocarpine, may cause morphologic and functional alteration in the aqueous outflow route. Thus, the intraocular pressure-lowering effects of isopropyl unoprostone may be associated with these changes in the aqueous outflow route, although we were unable to elucidate the exact mechanism underlying interindividual differences in the responsiveness to isopropyl unoprostone. Although our study shows only pressure-lowering effects at a short follow-up period (until 6 months), a previous report clearly demonstrated that the hypotensive effects of isopropyl unoprostone are stable for a long period.[26] Thus, in addition to previous reports,[8–14,26] our study shows that isopropyl unoprostone is a useful and safe medication for glaucomatous patients.

In conclusion, in this clinical investigation, we have reported that isopropyl unoprostone is a useful medication for the treatment of POAG, and that intraocular pressure level, history of cataract surgery, and age are prognostic factors for the responsiveness of intraocular pressure to this eyedrop.

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