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Influence of Topical Betaxolol and Timolol on Visual Field in Japanese Open-angle Glaucoma Patients

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Purpose: To assess the effects of topical betaxolol and timolol on the visual field in Japanese open-angle glaucoma (OAG) patients.

Methods: This study was a multicenter, 2-year, prospective, randomized and double-masked study. Tests using the Humphrey 30-2 perimeter program were conducted every 6 months and the data of 95 patients were analyzed using regression analysis. Estimated regression coefficients for mean deviation (MD), corrected pattern standard deviation (CPSD), and total deviation (TD) values clustered into 15 sectors were obtained for each treatment group.

Results: Estimated slopes (dB/year) for MD and CPSD showed no significant difference from zero in either group. However, in the betaxolol group, estimated slopes (dB/year) for two adjacent sectors in the inferior arcuate area were significantly positive ($P = .0135, .0116$) while in the timolol group, no significant difference from zero was seen in any of the sectors. IOP changes from baseline in the timolol group were greater than in the betaxolol group, although no statistical significance was seen at any of the examination times.

Conclusion: MD and CPSD showed no significant change in either group. In the betaxolol group, however, a significant trend in improvement of visual field performance was seen in the inferior arcuate subfield. Timolol reduced IOP more effectively than betaxolol in OAG patients. **Jpn J Ophthalmol 2003;47:199–207**

Key Words: Betaxolol, clinical study, glaucoma, timolol, visual field.

Introduction

The aim of glaucoma therapy is to maintain the patient's visual field. Intraocular pressure (IOP) is probably the most important risk factor for further deterioration of the visual field in glaucoma, and many previous studies, including randomized clinical trials, have demonstrated the effects of IOP reduction on the progression of glaucomatous visual field damage.[1–7] However, reduction in IOP is not necessarily effective in all cases, not only in open-angle glaucoma not associated with elevated IOP (normal-tension glaucoma), but also in open-angle glaucoma associated with elevated IOP,[4,5,7] and it has been recognized that IOP-independent damaging factors are also involved in the development of open-angle glaucoma.[8–12] Although IOP-independent damaging factors requiring intervention are not precisely defined, results of previous studies might shed some light on this issue. Systemic calcium antagonists may be beneficial at least temporarily in slowing the progression of visual field damage in a subset of open-angle glaucoma patients.[13–20] Several studies using topical betaxolol and timolol suggested that there might be dissociation between ocular hypotensive effects and slowing of visual field damage,[21–25] ie, topical betaxolol might have marginally better effects on glaucomatous visual field damage despite having less effect on IOP reduction than topical timolol.

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As far as previous population studies have demonstrated,[26–33] IOP is somewhat lower in Japanese than in white or black races, and the prevalence of normal-tension glaucoma is also thought to be higher. Thus, in Japanese glaucoma patients, management of IOP-independent damaging factors, if possible, may be of more clinical significance. The possibly beneficial effects of topical betaxolol,[21–25] which should be associated with less systemic effects than oral calcium antagonists, should be re-examined in this population. We carried out a multicenter, 2-year, prospective, randomized and double-masked study to estimate the effects of topical betaxolol and timolol on visual field performance and IOP in Japanese open-angle glaucoma patients, and we report the results in this communication.

Materials and Methods

The study was conducted at 21 centers (Table 1) throughout Japan, and the study protocol was approved by the institutional review board at each study center, with adherence to the tenets of the Declaration of Helsinki. Before enrollment, subjects received information regarding the study and written informed consent was obtained from each subject.

Subjects 20 years old or older with primary open-angle glaucoma or normal-tension glaucoma, and not meeting any of the exclusion criteria, were eligible to participate in the run-in period. Diagnostic criteria for normal-tension glaucoma are (1) nonoccludable open-angle; (2) IOP during follow-up consistently ≤21 mm Hg including 24-hour diurnal curve; (3) no apparent other systemic or local abnormalities which may be related to the optic nerve head change; (4) no apparent past history of hemodynamic crisis or elevated IOP; and (5) glaucomatous optic nerve head change and corresponding visual field damage as determined by the Humphrey Perimeter 30-2 program (Zeiss-Humphrey, San Leandro, CA, USA). Criteria for visual field damage adopted in the current study were 2 or more adjacent points of loss at 5 dB or more from the age-cor-

Table 1. Study Group

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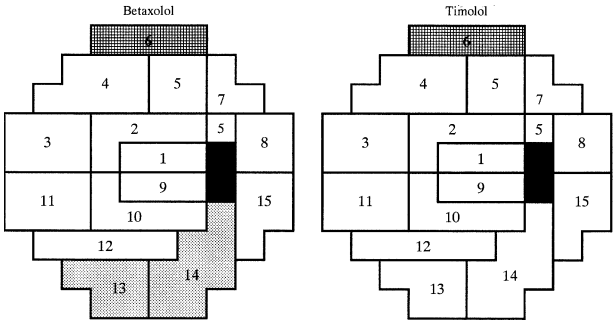

Figure 1. Distribution of sectors where estimated slope for clustered total deviation showed significantly positive value. ▩; excluded from analysis, ▩; significantly positive, □; not significantly different from 0. *P*-value is .0135 in sector 13 of betaxolol and 0.0116 in sector 14 of betaxolol, respectively.

rected normal reference value and/or 1 or more points of 10 dB loss and/or difference of 5 dB or more across nasal horizontal meridian at 2 or more adjacent points in the result obtained with the 30-2 program.[34] The following subjects were carefully excluded: subjects with angle-closure glaucoma, pigment dispersion, pseudoexfoliation, symptoms suggesting current or past uveitis, anterior or posterior synechia, ocular infection, retinal diseases that can affect the visual field, corneal abnormalities that can interfere with applanation tonometry, current use of contact lenses or past history of intraocular surgery except for laser surgery 6 months or more before enrollment. Patients contraindicated for topical β-blockers, such as those with bronchial asthma, chronic obstructive pulmonary disease, cardiac failure or second or third degree atrioventricular block and those using systemic adrenergic agonists or antagonists, calcium antagonists or vasodilatory drugs such as kallidinogenases, and women who were pregnant, breast-feeding or of child-bearing age were also excluded. Candidate subjects had to have experienced a visual field examination by the 30-2 program of the Humphrey Perimeter at least twice by reliable (fixation loss <20%, false-positive or -negative response <33%), and reproducible results with a mean deviation (MD) between −3 and −15 dB and/or abnormal corrected pattern

Table 2. Demographic Comparisons

Variable	Betaxolol	Timolol	Between Groups
Sex			
Male			
No. of patients (%)	16 (34.8)	18 (36.7)	
			NS†
Female			
No. of patients (%)	30 (65.2)	31 (63.3)	
Age (years)			
Mean ± SD	55.5 ± 10.6	57.9 ± 7.9	
Median (No. of patients)	56.0 (46)	59.0 (49)	NS‡
Range	28–74	34–72	
Diagnosis§			
POAG[3] No. of patients (%)	16 (34.8)	19 (38.8)	
			NS†
NTG[4] No. of patients (%)	30 (65.2)	30 (61.2)	
Mean deviation (dB)			
Mean ± SD	−6.516 ± 3.341	−5.739 ± 2.614	
Median (No. of patients)	−6.215 (46)	−5.630 (49)	NS‡
Range	−12.75–0.61	−12.06– −1.30	
Corrected pattern SD (dB)			
Mean ± SD	8.180 ± 4.193	7.900 ± 3.718	
Median (No. of patients)	8.145 (46)	8.400 (49)	NS‡;
Range	0.00–17.13	0.00–15.34	
Intraocular pressure (mm Hg)			
Mean ± SD	19.0 ± 2.7	18.0 ± 2.8	
Median (No. of patients)	18.0 (46)	18.0 (49)	NS‡;
Range	13–26	12–24	

*NS: not significant ($P > .05$).
†Fisher Exact test.
‡*t*-test.
§POAG: primary open-angle glaucoma, NTG: normal–tension glaucoma.

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standard deviation (CPSD) value with a *P* value of less than 5%. The corrected best visual acuity had to be 0.8 or better and spherical equivalent refraction had to be between −8 and +8 diopters.

During the run-in period, topical β-blockers or prostaglandin analogues were discontinued for at least 4 weeks, and topical pilocarpine, epinephrine or systemic carbonic anhydrase inhibitors for at least 2 weeks before baseline measurements were performed. Baseline measurements included IOP measurement by means of applanation tonometry, biomicroscopic examination, gonioscopy, posterior fundus, and optic nerve head examination with color fundus photographs, and visual field examination with the 30-2 program, which was repeated within 1 month if the result obtained was not reliable according to the above criteria.

Subjects were randomly allocated to either the 0.5% betaxolol or the 0.5% timolol group, according to the method of permuted blocks. The drug was instilled into both eyes as one drop twice a day for 2 years after the baseline measurements. Double masking of the study was confirmed by the controller. IOP measurement by means of applanation tonometry, biomicroscopic examination and posterior fundus and optic nerve head examination were performed every 1 to 3 months; visual field examination with the 30-2 program, every 6 months, and color fundus photographs were taken at 1 and 2 years. Patient compliance was checked at each visit. A patient was removed from the study when an investigator judged that it was impossible to continue the study because of adverse events or the progression of glaucoma.

Methods of Data Collection and Analysis

If both eyes of a patient met the above inclusion criteria, the eye with the worse MD was used for analysis. Primary variables were MD, CPSD, and total deviation (TD) values. TD values that are differences from the age-corrected reference value in dB at each test point of the 30-2 program were collected into 15 clusters (sectors in the visual field) according to the study of Suzuki et al.[35] TD data from the left eyes were converted into a mirror image of themselves. If the visual field result obtained was not reliable according the above criteria (fixation loss < 20%, false-positive or -negative response < 33%), the visual field examination was repeated within 1 month if possible. When the second visual field examination was not possible or also gave an unreliable result, the visual field data at that time point were excluded from analysis. The secondary variable was IOP. IOP data were excluded to maintain consistent data collection, if reliable visual field results were not obtained at that time point.

Table 3. Baseline of Total Deviation in Each Sector

	Betaxolol†	Timolol†	Between Groups (*t*-test)‡
Sector 1	−9.080 ± 8.619	−9.646 ± 9.627	NS
Sector 2	−10.900 ± 10.177	−8.331 ± 8.404	NS
Sector 3	−12.018 ± 9.566	−8.935 ± 7.402	NS
Sector 4	−8.407 ± 7.186	−5.370 ± 4.080	$P = .0123$
Sector 5	−7.783 ± 6.720	−4.865 ± 4.691	$P = .0155$
Sector 6§	–	–	–
Sector 7	−5.139 ± 6.971	−2.850 ± 4.159	$P = .0375$
Sector 8	−2.984 ± 3.827	−1.944 ± 2.608	NS
Sector 9	−2.101 ± 2.842	−2.177 ± 4.483	NS
Sector 10	−5.487 ± 8.305	−6.796 ± 8.452	NS
Sector 11	−7.301 ± 8.752	−8.687 ± 9.814	NS
Sector 12	−5.478 ± 6.981	−6.041 ± 6.648	NS
Sector 13	−4.704 ± 6.360	−3.878 ± 5.167	NS
Sector 14	−3.698 ± 4.877	−2.635 ± 2.594	NS
Sector 15	−2.457 ± 3.294	−2.241 ± 2.461	NS

*The central 30° visual field was sectored according to the method of Suzuki et al.
†Mean ± SD (dB).
‡NS: not significant ($P > .05$).
§Sector 6 was excluded from analysis.

In estimating the time course of change in MD and CPSD during the 2-year study period, we applied a regression analysis with a linear mixed model.[36] The model is as follows.

$$MD_{kij}(CPSD_{kij}) = (\beta_{0k} + b_{0ki}) + \beta_{1k} \times \mathrm{Time}_{ij} + \varepsilon_{kij} \quad (1)$$

Subscript *i* indicates subject; *j*: time point; *k*: treatment group; 0: intercept; 1: estimated slope of change; β represents fixed effect; b: random effect attributable to each individual, which was assumed to follow normal distribution; and ε , error. The estimated slope of change (dB/time) for MD or CPSD is given by β_1. The slope for each treatment group was estimated and the inter-group difference was examined. Also, the central 30° visual field was divided into 15 sectors, ie, the 74 test points of the 30-2 program were collected into 15 clusters, according to the study by Suzuki et al.[35] Using TD values within each cluster (sector in the visual field) as a group, the estimated slope of change of damage in each sector was calculated by sector. The model is as follows.

Table 4. Number of Eyes Analyzed

Group	Baseline	6-month	12-month	18-month	24-month
Betaxolol	46	34	33	30	27
Timolol	49	41	39	37	35

Table 5. Estimated Slope for Mean Deviation and Corrected Pattern Standard Deviation (dB/year)*

	Mean Deviation		Corrected Pattern Standard Deviation	
	Estimated Slope ± SE	Difference from Zero*	Estimated Slope ± SE	Difference from Zero†
Betaxolol	0.060 ± 0.175	NS	0.242 ± 0.130	NS
Timolol	0.004 ± 0.158	NS	0.204 ± 0.116	NS

*All slopes were estimated using linear mixed model.
†NS: Not significant ($P > .05$).

$$TD_{kmij} = (\beta_{0km} + b_{0kmi}) + \beta_{1km} \times \text{Time}_{mij} + \varepsilon_{kmij} \quad \ldots\ldots\ldots\ldots \quad (2)$$

where m (1, ...,5, 7, ...,15) indicates sector. Other subscripts are the same as in Equation (1). The estimated slope of change (dB/time) for damage in sector m is given by β_1 that is estimated using TD values of all test points in sector m. The uppermost sector consisting of four test points (sector 6 in Figure 1) was excluded from analysis, because the result in this sector may represent artificial effects by the upper lid rather than glaucoma-related damage.[35] This analysis was carried out for both the betaxolol and the timolol groups. Any difference from zero of the estimated slope was tested (*t*-test, two-tailed, $\alpha = 0.05$) without adjusting multiplicity. If the estimated slope in the betaxolol or the timolol group was significantly positive or negative, intergroup difference was also examined.

The change in IOP was compared between groups at each visit by visit using the *t*-test (two-tailed, $\alpha = 0.05$).

The software used was SAS Rel.6.12 (SAS Institute, Cary, NC, USA).

Results

Ninety-five patients who met the inclusion criteria including the results of baseline measurements were randomly allocated (46 for betaxolol and 49 for timolol) and treated between October 1996 and October 1999. The data obtained from these 95 patients were used for analysis.

The demographics for the study population are shown in Tables 2 and 3. There were no statistically significant differences ($P > .05$) between treatment groups for sex, age, diagnosis, or baseline values for MD, CPSD and IOP. For TD by sector, there were statistically significant differences at sectors 4, 5 and 7, but

Table 6. Estimated Slopes for Total Deviation in Each Sector (dB/year)*

	Betaxolol		Timolol		Between Groups (*t*-test)
	Estimated Slope ± SE	Difference from Zero	Estimated Slope ± SE	Difference from Zero	
Sector 1	0.43 ± 0.475	NS	0.334 ± 0.446	NS	
Sector 2	0.108 ± 0.290	NS	−0.336 ± 0.261	NS	
Sector 3	−0.134 ± 0.251	NS	−0.066 ± 0.217	NS	
Sector 4	−0.250 ± 0.207	NS	−0.222 ± 0.163	NS	
Sector 5	0.172 ± 0.239	NS	−0.101 ± 0.175	NS	
Sector 6	–		–		
Sector 7	0.196 ± 0.278	NS	−0.004 ± 0.210	NS	
Sector 8	−0.050 ± 0.191	NS	0.188 ± 0.156	NS	
Sector 9	0.307 ± 0.224	NS	0.051 ± 0.168	NS	
Sector 10	0.096 ± 0.210	NS	−0.121 ± 0.233	NS	
Sector 11	−0.208 ± 0.214	NS	−0.387 ± 0.226	NS	
Sector 12	−0.017 ± 0.213	NS	0.185 ± 0.203	NS	
Sector 13	0.537 ± 0.217	$P = .0135$	0.136 ± 0.199	NS	NS
Sector 14	0.346 ± 0.137	$P = .0116$	0.152 ± 0.107	NS	NS
Sector 15	−0.163 ± 0.177	NS	0.134 ± 0.147	NS	

*All slopes were estimated using linear mixed model. All the test points within each sector (from 3 to 8 points) werre included in the model without averaging.
Sector 6 was excluded from the analysis. Multiplicity was not adjusted.
†NS: not significant ($P > .05$).

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no significant difference was seen for any of the other sectors.

Eleven patients did not complete the study because of various adverse events. Cough, (betaxolol: 1); shortness of breath, heart flutter, erythema, blepharitis, (timolol: 1); uncontrolled IOP as judged by an investigator, (timolol: 1); withdrawal of consent to participate in the study and other reasons, (betaxolol: 5, timolol: 3). If a reliable visual field result could not be obtained, the data obtained at that time point were excluded. The number of patients included for analysis at each time point is shown in Table 4.

Estimated slopes (dB/year) for MD and CPSD in both groups are summarized in Table 5. No significant difference from zero was found for either MD or CPSD in both the betaxolol and timolol-groups, and no intergroup difference was seen. Estimated slopes (dB/year) for damage in each sector (1, 2, 3, ... to 15 except for 6) are summarized in Table 6. In the betaxolol group, two adjacent sectors in the inferior arcuate area showed significantly positive slopes, but no significant difference from zero was found for any other sector (Figure 1). In the timolol group, no significant difference from zero was seen in any of the sectors. For sectors 13 and 14, no significant intergroup difference was seen.

Mean IOPs are displayed in Figure 2 by treatment group and by study visit. Mean IOP changes from baseline in both groups are summarized in Table 7. The IOP reductions from baseline were statistically significant (paired *t*-test; $P < .0001$) at all visits in both groups. Mean IOP changes from baseline were greater with timolol (range, −3.1 to −3.7 mm Hg) than with betaxolol (range, −2.4 to −2.9 mm Hg), although no statistically significant difference between the groups was observed at any of the measurement visits.

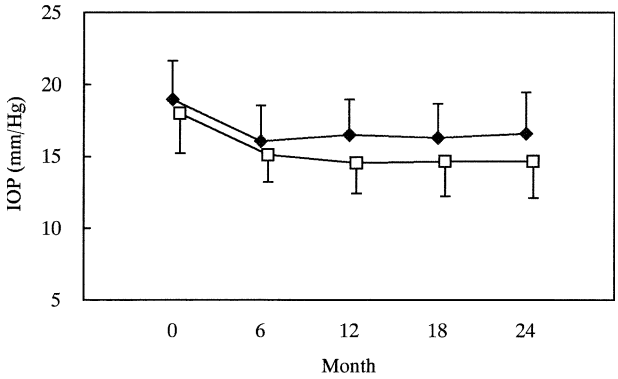

Figure 2. Intraocular pressure (mm Hg) during study period (mean ± SD). ◆; betaxolol, □; timolol.

Discussion

The purpose of glaucoma therapy is to maintain the patient's visual function. The primary objective of the present study was to reexamine the effects of topical betaxolol on the visual field in Japanese open-angle glaucoma patients whose mean baseline IOP was considerably lower than that in studies from other countries examining the same issue. When normal-tension glaucoma patients with a mean untreated IOP of 16 mm Hg or higher were included, the baseline IOP averaged 18.5 mm Hg in the present subjects, while that in these previous studies averaged 23–24 mm Hg.[21–25] Thus, the contribution of IOP-independent damaging factors to the progression of visual field damage, if they exist,[8–12] was thought to be relatively more significant in these Japanese subjects than in the subjects in the previous studies. The possible therapeutic effects of betaxolol on IOP-independent damaging factors in open-angle glaucoma may be more sensitively detected in the present Japanese subjects.

In agreement with previous results including those obtained in Japan,[37,38] topical betaxolol was less effective than topical timolol in reducing IOP. The estimated slope of change in MD or CPSD showed no significant difference from zero not only in the timolol-treated eyes, but also in the betaxolol-treated eyes, and topical betaxolol and timolol were thought to be similar in maintaining the classical visual field indices, MD and CPSD, as far as the present study period of 2 years is concerned.

Because of the recognized beneficial effect of IOP reduction in open-angle glaucoma,[1–3] a placebo-control group could not be established. Previously, we studied the effects of oral brovincamine in normal-tension glaucoma patients.[20] When we used the time course data of the visual field (30-2 program) during the 2-year study period to calculate the power, the difference in estimated slope for MD of 0.5 dB/year from zero was detected with α of 0.05 and $(1-\beta)$ of more than 0.8 for a sample size of 40 patients and visual field tests at intervals of 6 months for 2 years.

The present result obtained for MD in patients receiving betaxolol or timolol is compatible with those reported by Drance[25] or Kaiser et al,[23] but different from those of Collignon-Brach[22] or Tasindi et al[24] who found significant improvement of MD in the betaxolol-treated group. Because MD is not useful in detecting local sensitivity changes, we clustered test points of the 30-2 program of the Humphrey Perimeter according to the study of Suzuki et al[35] into 15 clusters (sectors in the visual field), complying with

Table 7. Change of Intraocular Pressure During Study Period (mm Hg)

Treatment	6-month	12-month	18-month	24-month
Betaxolol*	−2.9 ± 3.0	−2.7 ± 2.5	−2.8 ± 2.4	−2.4 ± 2.4
Timolol*	−3.1 ± 2.6	−3.7 ± 2.7	−3.5 ± 2.3	−3.5 ± 2.5
Difference (*t*-test)	0.2	1.0	0.8	1.1
	$P = .7397$	$P = .1039$	$P = .2006$	$P = .0901$

*Mean ± SD.

the anatomy of retinal nerve fiber bundles. In the timolol-treated eyes, the estimated slope of change in damage showed no significant difference from zero in any of the sectors examined. On the other hand, in the betaxolol-treated eyes, it was significantly positive in two adjacent sectors located in the inferior arcuate area, suggesting visual field performance improvement during the study period in this subfield. Since statistical analysis was applied in each of the 14 sectors studied, an overall α error for the above result may not be warranted. If TD values in each of the 14 sectors are independent, ie, the intercorrelation is zero, the *P* value can be corrected by Bonferroni's method. In the glaucomatous visual field, however, there is a high intercorrelation between the damage and visual field performance in the 14 sectors complying with the anatomy of the retinal nerve fiber bundles,[35] and it is difficult to correct the *P* value in such cases. A significantly positive slope in the two adjacent sectors complying with the anatomy of the retinal nerve fiber bundles suggests that this finding is not attributable only to statistical fluctuation.

Improvement in the visual field performance in the inferior arcuate area in the betaxolol-treated eyes may be interesting in view of the following previous studies. Primary open-angle glaucoma patients with predominantly inferior visual field damage are reportedly more likely to have diabetes,[39,40] which suggests that a vascular factor is more likely to be responsible for the inferior visual field damage as in the case of nonarteritic ischemic optic neuropathy.[41] Although not always confirmed, it has been reported that normal-tension glaucoma is more commonly associated with damage in the inferior hemifield than is the case with high tension-glaucoma.[42,43] There have been several reports suggesting the beneficial effects of topical betaxolol on the retinal, optic nerve head or retrobulbar circulation in humans,[44–47] and Yu et al found that betaxolol at concentrations higher than 10^{-12} M caused dilation of endothelin-1 preconstricted, isolated, and perfused human retinal arterioles.[48] Taken together with these previous findings, the possible relation of the vascular effects of betaxolol to the present findings cannot be ruled out. Several in vitro studies have demonstrated the neuroprotective effects of betaxolol at relatively high concentrations.[49–52] However, it remains to be clarified whether topically applied betaxolol reaches the retina or optic nerve head in human eyes at the effective concentrations reported in the in vitro studies.

The sample size was too small and the duration of observation was too short to draw any conclusions on the differences between betaxolol and timolol in their effect on the visual field. Nevertheless, a trend of visual field performance improvement in the inferior arcuate subfield in Japanese open-angle glaucoma patients receiving betaxolol warrants further studies to elucidate IOP-independent damaging factors which are to be treated to slow down the progression of open-angle glaucoma.

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