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Effect of a Single Drop of Latanoprost on Intraocular Pressure and Blood-Aqueous Barrier Permeability in Patients with Uveitis

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The purpose of our study is to evaluate the effect of a single drop of latanoprost on the intraocular pressure and blood-aqueous barrier permeability in 8 patients with uveitis. The degree of inflammation was determined by the intensity of aqueous flare measured with a laser flare cell meter every 2 hours from 11:00 to 17:00 hours for 2 days. Intraocular pressure was measured at 11:00 and 17:00 hours with a Goldmann applanation tonometer on both days. Patients were given one drop of 0.005% latanoprost at 11:00 hours on day 2 and results were compared with day 1 when latanoprost was not administered. There was no significant difference in the intensity of aqueous flare or intraocular pressure between day 1 and day 2. A single drop of latanoprost had little effect on intraocular pressure and aqueous flare intensity in patients with uveitis.

Latanoprost is a prostaglandin (PG) $F_{2\alpha}$ derivative and has a strong effect on lowering the intraocular pressure (IOP) in patients with primary open angle glaucoma (POAG) and in normal eyes (5,6). The question arises whether latanoprost can be used in patients with ocular hypertension secondary to uveitis because ocular hyperemia and irritable symptoms are well known side effects of prostaglandins and prostaglandin analogues (2). In addition, it has been shown that the PG concentration in the aqueous humor is increased in patients with uveitis (9), and that topical application of PGE_2 induces a breakdown of the blood-aqueous barrier in rabbit eyes (20). It is generally believed that there is a close association between prostaglandins and ocular inflammation. However, latanoprost was designed to reduce the IOP with minimal inflammatory side effects (5,6). And it has been shown that latanoprost can reduce the IOP in normal eyes and POAG patients without altering the blood-aqueous barrier permeability (5,6). Recently, several reports have shown a recurrence or enhancement of ocular inflammation after topical application of latanoprost to susceptible eye (4,11,19). Thus, the effect of latanoprost on the blood-aqueous barrier in eyes with inflammation may be distinct from its action in eyes without inflammation. The increase of inflammatory reactions in eyes often leads to the visual impairment of patients. It is important to perform a single drop examination before starting long term studies. We therefore examined the effects of a single drop of latanoprost on IOP and on the blood-aqueous barrier permeability in patients with uveitis using a laser flare cell meter.

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MATERIALS AND METHODS

The study protocol was reviewed and approved by the Osaka National Hospital Ethics Committee. The purpose of the study was fully explained and informed consent was obtained from all patients participating in this study. The conduct of the study conformed to the Declaration of Helsinki and its subsequent amendments. Subjects with corneal opacities and edema, with mature cataract that interfered with the measurement of aqueous flare and IOP, patients with previous laser treatment, and those who had undergone intraocular surgery in the previous 6 months were excluded. Patients using topical and oral carbonic anhydrase inhibitors, topical beta-adrenergic blockers, and atropine eye drops were included.

We studied 8 eyes of 8 patients (5 men and 3 women) aged 24-68 years (mean ± SD, 47.9 ± 15.5 years) (Table I). All of the patients had a history of glaucoma therapy and were scheduled to receive surgery for glaucoma or cataract secondary to uveitis. The eyes scheduled for receiving surgery were served for the examination. None of the patients had previously received latanoprost therapy. Uveitis was caused by Behçet's disease (n = 3), Vogt-Koyanagi-Harada syndrome (n = 3), sarcoidosis (n = 1) and unknown (n = 1). Inflammation had been well controlled by therapy for more than 3 months in 6 patients, but had only just cleared in two patients (cases #2 and #3), at the time of this study following an acute exacerbation of uveitis. All patients were receiving topical steroids and 4 were receiving oral steroids. Two of three patients (case #2 and #3) with Behçet's disease were treated with colchicine in addition to oral steroid. The anterior chamber angle in case #8 was not examined. Approximately 50% of chamber angle was closed by peripheral anterior synechia (PAS) in case #7. All other patients had widely opened angle without any PAS.

TABLE I. Clinical characteristics of patients.

Patient no.	Age (yr)	Gender	Disease type	Steroids		Uveitis activity	Combined therapy
				topical	oral		
1	32	F	Behçet's disease	0.1% betametha 5 times/day	pred 30mg	silent	
2	35	M	Behçet's disease	0.1% betametha 5 times/day	betametha 30mg	active	beta+tCAI+atropine +colchicine
3	24	M	Behçet's disease	0.1% betametha 5 times/day	pred 30mg	active	colchicine
4	55	M	VKH syndrome	0.1% betametha 3 times/day	–	silent	beta+oCAI
5	54	M	VKH syndrome	0.1% betametha 4 times/day	–	silent	beta+uno+oCAI
6	54	F	VKH syndrome	0.1% betametha 1 time/day	–	silent	
7	68	F	sarcoidosis	0.1% fluoro 3 times/day	betametha 5 mg	silent	beta+uno
8	61	M	unknown	0.1% betametha 3 times/day	–	silent	
Mean age (± SD)	47.9 ± 15.5						

Abbreviations: F, female; M, male; SD, standard deviation; VKD, Vogt-Koyanagi-Harada; betametha, betamethasone sodium phosphate; furuoro, fluorometholon; pred, prednisolone; beta, beta adrenergic blocker; uno, unoprostone; tCAI, topical carbonic anhydrase inhibitor; oCAI, oral carbonic anhydrase inhibitor.

On day 1, the aqueous flare intensity was measured every 2 hours from 11:00 to 17:00 hours with a laser flare cell meter (FC 1000; Kowa, Tokyo) without the use of mydriatic agents. To normalize the flare counts; data were expressed as percentages of the flare count at 11:00 hours taken as 100%. For statistical analysis of the aqueous flare intensity, the area under the curve (AUC) of the flare intensity graph in arbitrary units was calculated. The IOP was measured with a Goldmann applanation tonometer on both days after the aqueous flare measurement at 11:00 and 17:00 hours.

On day 2, patients were given a single drop of 0.005% latanoprost immediately after tonometry at 11:00 hours, and the IOP and the flare intensity were measured as on day 1. The data from day 1 and day 2 were compared.

All of the data are presented as the mean ± standard deviation (SD). Statistical analysis was carried out using Wilcoxon signed rank test. Differences were accepted as significant when $P < .05$.

TABLE Ⅱ. Changes in IOP.

Patient no.	IOP (mmHg)			
	day 1		day 2	
	11:00 hr	17:00 hr	11:00 hr	17:00 hr
1	22	24	21	17
2	20	26	18	15
3	16	16	17	18
4	35	42	28	32
5	31	28	30	42
6	16	11	11	9
7	24	32	22	25
8	15	14	14	11
Mean (± SD)	22.4 ± 7.3	24.1 ± 10.3	20.1 ± 6.5	21.1 ± 11.2

Abbreviations: IOP, intraocular pressure; SD, standard deviation.

RESULTS

On day 1, the mean IOPs at 11:00 and 17:00 hours were 22.4 ± 7.3 and 24.1 ± 10.3 mmHg, and on day 2, the mean IOPs at 11:00 and 17:00 hours were 20.1 ± 6.5 and 21.1 ± 11.2 mmHg, respectively (Table Ⅱ). Mean IOP 6 hours after latanoprost instillation did not significantly differ from that before instillation on day 2 ($P = .833$), and the difference between the IOP at 17:00 hours on days 1 and 2 was also not significant ($P = .234$).

The flare intensity in normal human eyes are usually under 10 photon count/second (pc/sec) (12). The flare intensity in our subjects at 11:00 on day 1 ranged from 11.0 pc/sec to 162.0 pc/sec (37.6 ± 50.8 pc/sec), and the flare intensity at 11:00 on day 2 were same as day 1 (Table Ⅲ). The AUC of the aqueous flare intensity on day 2 was comparable to that on day 1. The AUC of aqueous flare intensity on day 1 was 3.78 ± 0.34 (arbitrary units) and the AUC on day 2 was 3.84 ± 0.46 ($P = .575$). The flare intensity was not altered to a statistically significant degree following latanoprost administration (Fig.1, Table Ⅲ). Furthermore there were no anomalous inflammatory changes on biomicroscopy after latanoprost instillation.

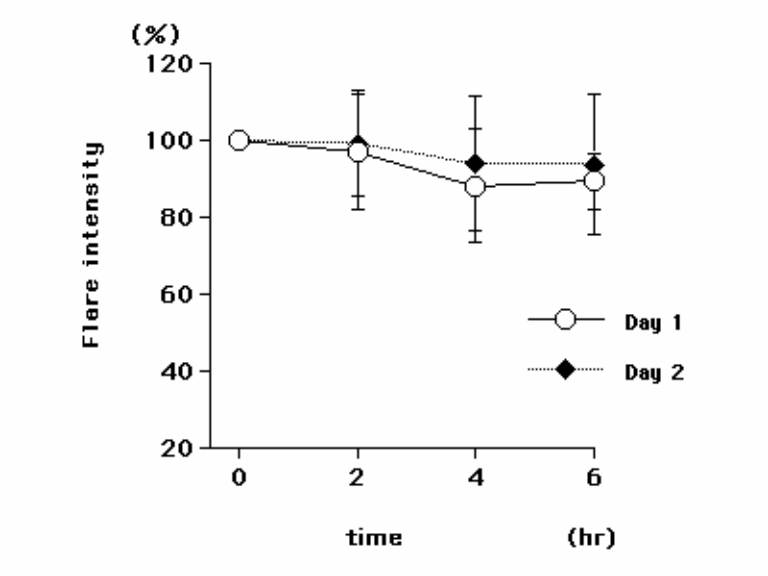

FIG. 1. Changes of flare intensity on day 1 and day 2. There were no significant changes between day 1 and day 2.

TABLE Ⅲ. Changes in flare intensity.

Patient no.	Flare intensity				Area under the curve†	
	day 1		day 2		day 1	day 2
	11:00 hr	17:00 hr	11:00 hr	17:00 hr		
1	14.4	13.2	10.1	6.5	3.91	3.19
2	11.0	9.1	8.8	6.9	3.34	3.50
3	28.3	27.9	27.4	32.0	4.35	4.64
4	11.3	8.6	12.6	11.4	3.54	3.69
5	28.8	27.8	25.5	23.0	3.84	3.76
6	162.0	148.8	142.6	167.9	3.58	4.31
7	19.5	17.1	16.0	16.0	3.56	4.00
8	25.8	23.0	19.0	17.5	4.13	3.63
Mean (± SD)	37.6 ± 50.8	34.4 ± 46.8	32.8 ± 44.9	35.1 ± 54.3	3.78 ± 0.34	3.84 ± 0.46

Abbreviations and symbols: †, arbitrary units; SD, standard deviation.

DISCUSSION

Latanoprost is one of the most effective ocular hypotensive agents currently available (3). After latanoprost, the IOP in many POAG patients decreases below the targeted pressure and glaucoma surgery is not required. The question arose whether patients with ocular hypertension secondary to ocular inflammation could also benefit from latanoprost therapy. It has been reported that latanoprost is effective and safe in lowering IOP in patients with POAG and in normal volunteers without causing any alteration of blood-aqueous barrier permeability (5,6). It has been shown that latanoprost does not cause an accumulation of inflammatory cells in the anterior segment of rabbit eyes (8), or affect the regulation of vascular tone or capillary

permeability in monkey eyes (16). However, the effect of latanoprost on aqueous flare intensity and IOP in patients with uveitis has not been fully examined. There have been reports of patients that developed anterior uveitis after starting latanoprost therapy (4,11,19). Contrary to those reports, Smith et al. (15) treated ocular hypertensive patients secondary to uveitis with latanoprost and reported that latanoprost therapy did not seem to enhance inflammation even in patients with uveitis at the active stage. The association of uveitis to latanoprost remains uncertain. In these reports the severity of inflammation was evaluated with slit lamp using a grading scale that was subjectively determined to some degree. However, the Kowa laser flare cell meter facilitates as objective determination of the changes in flare intensity in the anterior chamber (12).

We previously used the laser flare cell meter to test whether there were changes in aqueous flare intensity after a single application of latanoprost in rabbit eyes with endotoxin-induced uveitis (7). We selected rabbits, as they are more sensitive to irritating stimuli than humans (1). A single drop of latanoprost had little effect on blood-aqueous barrier permeability in normal rabbit eyes or eyes with experimentally-induced uveitis (7). In this study, we performed a preliminary small single drop study before conducting a long-term examination in a large number to minimize the risk of further damage in patients with uveitis from the uncertain side effect of latanoprost. We examined the effect of a single drop of latanoprost on aqueous flare intensity and IOP in patients with uveitis. The flare intensity in our subjects ranged from almost normal intensity to more than 10 times higher than normal. All of our patients were under steroid therapy. Our results demonstrated that latanoprost did not produce a significant change in aqueous flare intensity. There was no case that responded anomalously to latanoprost instillation. It might therefore be concluded that a single drop of latanoprost has little effect on the blood-aqueous barrier in human eyes with inflammation. But, we must remember these results were obtained under the influence of steroid therapy.

However, we did not show a significant IOP reduction after a single drop of latanoprost. There are two routes for aqueous humor drainage in human eyes. One route is the conventional outflow through the trabecular meshwork and Schlemm's canal to the aqueous veins. The second route is called the uveoscleral outflow route in which the aqueous humor leaves the eye from the chamber angle through the ciliary muscle bundles to the suprachoroidal space, then drains via the sclera or vortex veins (13). Latanoprost reduces IOP by increasing uveoscleral outflow (10,18). In POAG and ocular hypertensive patients, 0.005% latanoprost decreased IOP significantly from a mean baseline pressure of 23.1 ± 2.3 mm Hg by over 4 mm Hg ($P < .01$) at 4 hours after application (6). In normotensive Japanese subjects, topical 0.006 % latanoprost significantly decreased IOP by 2 mm Hg at 4 hours ($P < .001$) and the effect was maintained for 24 hours (5). Alterations of the outflow pathway by inflammation, eg, PAS and the obstruction of outflow pathway by inflammatory debris, are the mechanisms that increase IOP in patients with uveitis (14). The entrance to both the trabecular and uveoscleral outflow pathway is at the anterior chamber angle. Inflammatory debris or PAS at the anterior chamber angle can obstruct not only the trabecular meshwork but also uveoscleral outflow, and thus, disturb the action of latanoprost. Therefore, the magnitude of IOP reduction in this study may be less than in other studies on POAG patients without inflammation and in normal eyes. Smith et al. (15) also showed the IOP in patients with active uveitis remained unchanged after latanoprost.

We found a single drop of 0.005% latanoprost did not have a statistically significant effect on IOP or the aqueous flare intensity in patients with uveitis. The ocular hypotensive effect of latanoprost increases with time (17), and the prolonged use of latanoprost may change blood-aqueous barrier permeability. Daily application of $PGF_{2\alpha}$ isopropyl ester and

PGE_2 to rabbit eyes caused an initial increase in aqueous flare. However, the increased aqueous flare gradually decreased day by day (8). Glaucoma patients generally use eye drops over the long-term to achieve an IOP decrease. It is not possible to draw conclusions on the effect and safety of latanoprost from this single-drop study. Long-term and careful observations are necessary to obtain the answer. However, the results of this study do not exclude the possibility of using latanoprost for ocular hypertensive patients with uveitis. It is certainly worth exploring the possibility of using latanoprost in patients with uveitis, because a single drop of latanoprost did not induce any harmful results.

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