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CLINICAL INVESTIGATION

Twenty-Four-Hour Ocular Hypotensive Effects of 0.0015% Tafluprost and 0.005% Latanoprost in Healthy Subjects

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Abstract

Purpose: To compare the intraocular pressure (IOP) reduction over 24 h achieved with tafluprost (0.0015%) with that achieved with latanoprost (0.005%).

Methods: Twenty-seven healthy volunteers were studied. After a 24-h IOP baseline measurement was taken, one ophthalmic solution was applied to the right eye daily for 7 days. The drug was then withdrawn for 2 weeks. The other agent was then applied to the left eye in the same manner. IOP was measured every 3 h for 24 h on the seventh day of treatment.

Results: The 24-h IOP after 7 days' treatment with latanoprost decreased from 11.5 mmHg at baseline to 9.7 mmHg (–1.8 mmHg) and that with tafluprost from 11.8 to 9.8 mmHg (–1.9 mmHg). Tafluprost was statistically more effective after 24 h ($P = 0.007$; paired t test). The number of subjects with a 24-h mean IOP reduction of <10% was 8/27 (29.6%) with latanoprost versus 4/27 (14.8%) with tafluprost. The incidence of conjunctival hyperemia with latanoprost was 4/27 (14.8%) and that with tafluprost was 8/27 (29.6%).

Conclusion: The overall efficacies of the two agents were not different, but tafluprost was associated with a greater reduction in IOP at 24 h after administration. Tafluprost showed a higher rate of conjunctival hyperemia. **Jpn J Ophthalmol** 2010;54:286–290 © Japanese Ophthalmological Society 2010

Keywords: intraocular pressure, latanoprost, tafluprost

Introduction

Latanoprost[1,2] and other prostaglandin (PG) analogs have ocular hypotensive effects and are widely used to treat glaucoma, including cases with low intraocular pressure (IOP).[3–7] Latanoprost 0.005% is now one of the most widely prescribed drugs for treating glaucoma.

Tafluprost[8] is a novel PG F2α analog that is difluorinated at position 15. The 0.0015% preparation was recently introduced in Japan and in parts of Europe, but few studies have compared its effects with those of latanoprost 0.005%. In mice[9] and monkeys,[10] tafluprost 0.005% has shown better ocular hypotensive effects than latanoprost 0.005%. However, to date only one phase I study has been reported in humans.[11] In that study, tafluprost 0.005% demonstrated better hypotensive effects than latanoprost 0.005% in humans with a baseline IOP of 14–16 mmHg. Tafluprost 0.0025% had greater ocular hypotensive effects than latanoprost at 24 h after administration.

However, the concentration of commercially available tafluprost is 0.0015%, and 24-h IOP measurements were not performed using this concentration in the parallel-design trial described above.

Therefore, we performed a crossover trial with both drugs in 27 healthy subjects to measure and compare their

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IOP every 3 h over a 24-h period after 7 days of administration of each drug, with a 2-week washout period between each treatment period.

Methods

This study was a prospective, randomized, open and active-controlled trial. We originally enrolled 30 Japanese volunteers. However, two subjects withdrew during the study owing to upper respiratory infection, and one withdrew for personal reasons. Therefore, 27 subjects (17 men, 10 women; average age, 22.2 ± 2.8 years; range, 19–34 years) completed the protocol. The study protocol was approved by the Institutional Review Board at Hiroshima University Graduate School of Biomedical Science (clinical trial registration number UMIN000001693). All subjects gave their written informed consent.

The subjects initially underwent an ophthalmological examination that included best-corrected visual acuity, IOP measurement using a Goldmann tonometer, slit-lamp biomicroscopy, funduscopy, and testing with the Humphrey Field Analyzer 30-2 SITA-fast program. We excluded subjects with disorders detected by the ophthalmological examination, a history of ocular diseases, or a history of intraocular operations, and those suspected of being allergic to the study drugs or incipients, and those who could not follow the study protocol or who used systemic or topical medications with potential effects on IOP. No subject was excluded on the basis of these exclusion criteria. We obtained both medications commercially, latanoprost 0.005% (Xalatan, Pfizer, Tokyo, Japan) and tafluprost 0.0015% (Tapros, Santen, Osaka, Japan). We randomly divided the subjects into two groups of equal numbers and administered either latanoprost or tafluprost according to the study schedule (Fig. 1).

Before the first treatment period, we measured the subjects' baseline 24-h IOP and instructed them to administer one drop into the right eye every day at 7 p.m. for 7 days. A reminder e-mail was sent to the subjects' cellular phones every day at 7 p.m., and the participants administered the eye drops themselves. We performed slit-lamp biomicroscopy to evaluate ocular adverse events. We also questioned the subjects about subjective changes and the number of drops they missed during the 7 days.

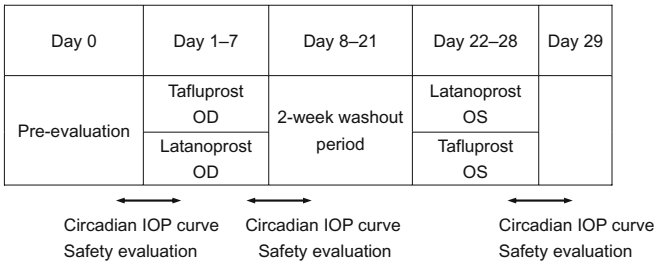

Figure 1. Study design. Twenty-four-hour intraocular pressure was measured starting at 7 p.m., and was performed on day 0 as baseline and on days 7 and 28 to evaluate each drug. *OD*, right eye; *OS*, left eye; *IOP*, intraocular pressure.

After completing the first treatment period, the subjects waited for 2 weeks before starting the second treatment period. The second treatment, according to the study schedule, was administered into the left eye to avoid any carry-over effects (Fig. 1).

Both at baseline and on day 7 of each treatment period, we measured the IOP, starting at 7 p.m., every 3 h (7 p.m., 10 p.m., 1 a.m., 4 a.m., 7 a.m., 10 a.m., 1 p.m., 4 p.m., and 7 p.m.) for 24 h. IOP was measured with calibrated Goldmann applanation tonometers, with the subjects in a sitting position, including the measurements at 1, 4, and 7 a.m. Two specialists examined the subjects, and each subject was measured by the same examiner with the same tonometer. The reduction in IOP was calculated from the baseline IOP in the same eye as the treatment.

The study was calculated detect up to 80% of a 1.2-mmHg difference in the mean IOP between the two dependent groups, assuming a standard deviation of 2 mmHg and an α-value of 0.05. We performed two-tailed tests of all data, and a value of $P < 0.05$ was considered statistically significant. The 24-h IOP curves were compared by repeated measures analysis of variance (ANOVA), and a paired *t* test was used to compare each time point within the ANOVA. Bonferroni's correction was used to adjust the *P* values for multiple comparisons among individual time points. IOPs within the first 12 h after administration (10 p.m., 1 a.m., 4 a.m., and 7 a.m.) were identified as one data group, and those in the second 12 h (7 p.m., 10 a.m., 1 p.m., 4 p.m., and 7 p.m.) were considered as a second data group. We used $P = 0.05/4$ as the significance level for the first group and $= 0.05/5$ (α/n) for the second group. The data were grouped to prevent the Bonferroni correction from providing extremely conservative *P* values.[12] Paired *t* tests were used to compare the maximum and minimum IOPs, IOP fluctuation, the first and second 12-h mean IOPs, and the 24-hour mean IOP. The number of adverse events and the number of subjects who showed a response rate of <10% were analyzed by Fisher's exact test. All analyses were performed with StatView version 5.0 (SAS, Cary, NC, USA).

Results

All 27 subjects completed both treatment periods without missing any dose. The mean baseline IOP at each time point ranged from 9.6 to 14.0 mmHg. The mean baseline IOP for latanoprost over 24 h was 11.5 ± 2.1 mmHg (range, 8.9–15.7 mmHg) and that for tafluprost was 11.8 ± 2.2 mmHg (range, 8.8–15.6 mmHg). The mean IOP at each time point after administration ranged from 7.6 to 12.0 mmHg. The mean IOP over 24 h after administration with latanoprost was 9.7 ± 2.1 mmHg (range, 7.0–13.0 mmHg) and that after tafluprost was 9.8 ± 2.2 mmHg (range, 7.1–13.0 mmHg) (Table 1, Fig. 2). Therefore, the baseline to day 7 change in the 24-h IOP was –1.8 mmHg [95% confidence interval (CI), –1.4, –2.2] with latanoprost and –1.9 mmHg (95% CI,

Table 1. Absolute intraocular pressures (mmHg)

Time	Latanoprost		Tafluprost	
	Baseline	Day 7	Baseline	Day 7
7 p.m.	12.3 ± 2.2	10.0 ± 2.0	13.0 ± 2.5	10.8 ± 2.1
10 p.m.	11.8 ± 1.9	9.5 ± 1.6	12.2 ± 1.8	10.3 ± 1.6
1 a.m.	10.9 ± 2.0	8.6 ± 1.9	11.2 ± 2.1	9.4 ± 1.8
4 a.m.	11.0 ± 2.3	9.0 ± 1.9	11.0 ± 2.3	9.8 ± 2.7
7 a.m.	11.0 ± 1.8	9.4 ± 2.0	10.9 ± 1.7	10.0 ± 2.8
10 a.m.	11.4 ± 2.1	10.3 ± 2.2	11.8 ± 2.1	9.7 ± 2.2
1 p.m.	11.4 ± 1.9	10.1 ± 2.2	11.6 ± 1.9	9.4 ± 1.9
4 p.m.	11.6 ± 2.4	9.7 ± 2.0	11.8 ± 2.3	9.4 ± 1.7
7 p.m.	11.8 ± 2.1	10.6 ± 2.2	12.4 ± 2.1	9.7 ± 2.1
24-h	11.5 ± 2.1	9.7 ± 2.1	11.8 ± 2.2	9.8 ± 2.2
Maximum	14.0 ± 1.7	12.0 ± 1.7	14.0 ± 1.8	12.0 ± 2.1
Minimum	9.6 ± 1.6	7.7 ± 1.5	9.8 ± 1.7	7.6 ± 1.4
Fluctuation	4.0 ± 1.1	4.5 ± 1.2	4.3 ± 1.6	4.7 ± 1.4

Values are means ± SD; $n = 27$.

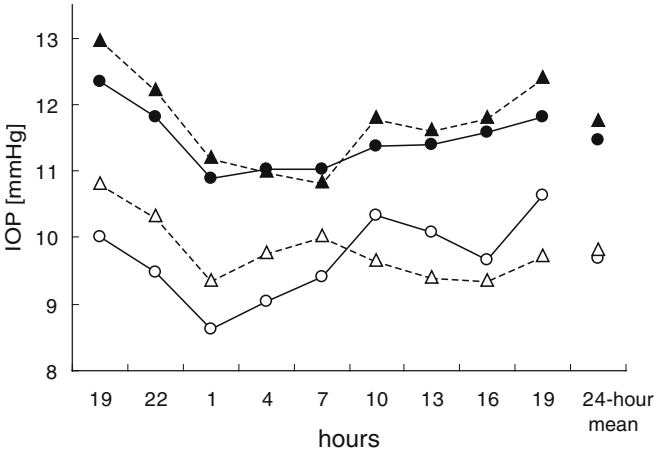

Figure 2. Twenty-four-hour IOP at baseline and after treatment with latanoprost and tafluprost. ●, latanoprost baseline; ○, latanoprost day 7; ▲, tafluprost baseline; △, tafluprost day 7.

–1.5, –2.3 mmHg) for tafluprost, corresponding to a 16.3% (95% CI, 12.9%, 19.6%) decrease for tafluprost and a 15.2% (95% CI, 11.8%, 18.6%) decrease for latanoprost.

Comparison of the 24-h IOP curves revealed a statistically significant difference between the two medications ($P = 0.0064$) (Table 2, Fig. 3). Latanoprost had a greater ocular hypotensive efficacy for the first 12 h ($P = 0.018$), whereas tafluprost had a greater efficacy for the second 12 h of the measurement period ($P = 0.003$) (Table 2, Fig. 3).

Tafluprost was superior to latanoprost at 24 h after administration (at 7 p.m., the end of the 24-h curve) (Table 2, Fig. 3). The P values at 10 a.m. and 1 p.m. exceeded 0.05/4 (α/n), which we did not consider a significant difference. No differences between the two medications were detected in the changes in the 24-h mean IOP, in maximum or minimum IOP, or in IOP fluctuation (Table 2).

Approximately 30% of the subjects (8/27) treated with either tafluprost or latanoprost (8/27) showed a reduction in the 24-h mean IOP of ≥20%. On the other hand, eight

Table 2. Baseline to end-point changes in intraocular pressure (mmHg) at each time point ($n = 27$)

Time	Latanoprost Mean (95% CI)	Tafluprost Mean (95% CI)	P value
7 p.m.	–2.3 (–3.3, –1.4)	–2.1 (–3.2, –1.1)	0.658
10 p.m.	–2.3 (–3.1, –1.6)	–1.9 (–2.5, –1.2)	0.286
1 a.m.	–2.3 (–3.1, –1.5)	–1.9 (–2.8, –0.9)	0.346
4 a.m.	–2.0 (–2.9, –1.1)	–1.2 (–2.1, –0.4)	0.127
7 a.m.	–1.6 (–2.4, –0.9)	–0.8 (–1.6, 0.0)	0.116
10 a.m.	–1.0 (–1.9, –0.1)	–2.1 (–3.0, –1.3)	0.047
1 p.m.	–1.3 (–2.0, –0.3)	–2.2 (–3.1, –1.4)	0.025
4 p.m.	–1.9 (–2.7, –1.2)	–2.4 (–3.2, –1.7)	0.114
7 p.m.	–1.2 (–2.0, –0.4)	–2.6 (–3.5, –1.9)	0.007*
First 12-h mean	–2.1 (–2.5, –1.6)	–1.4 (–1.9, –1.0)	0.018*
Second 12-h mean	–1.6 (–2.0, –1.1)	–2.3 (–2.8, –1.8)	0.003*
24-h mean	–1.8 (–2.2, –1.4)	–1.9 (–2.3, –1.5)	0.328
Maximum	–1.4 (–2.0, –0.7)	–1.7 (–2.5, –1.0)	0.401
Minimum	–1.9 (–2.4, –1.3)	–2.2 (–2.7, –1.6)	0.311
Fluctuation	0.5 (–0.2, 1.2)	0.4 (–0.5, 1.4)	0.869

First 12 h, 10 p.m., 1 a.m., 4 a.m., and 7 a.m.; second 12 h, 7 p.m., 10 a.m., 1 p.m., 4 p.m., and 7 p.m.
CI, confidence interval.
*Statistically significant difference after Bonferroni adjustment.

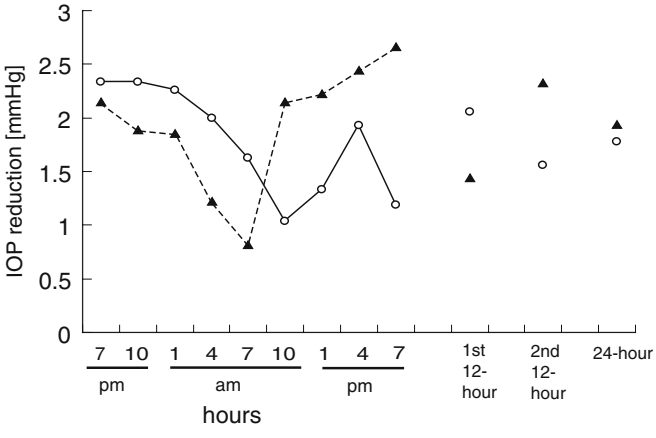

Figure 3. Twenty-four-hour intraocular pressure reduction curves after treatment with latanoprost and tafluprost. ○, latanoprost; ▲, tafluprost. There is a significant difference between the two curves ($P = 0.0064$; analysis of variance with repeated measures). Latanoprost had a better effect on reducing the IOP in the first 12 h (10 p.m., 1 a.m., 4 a.m., and 7 a.m.), whereas tafluprost was better in the second 12 h (starting at 7 p.m., then at 10 a.m., 1 p.m., 4 p.m., and again at 7 p.m.).

subjects treated with latanoprost (30%) and four treated with tafluprost (15%) experienced a 24-h IOP reduction of <10% (Fig. 4). However, the between-group difference was not significant ($P = 0.327$, Fisher's exact test). Five of the eight subjects with a response rate of <10% to latanoprost showed response rates of >10% to tafluprost. Meanwhile, one of the four subjects with a response rate of <10% to tafluprost showed response rates of >10% to latanoprost.

Both medications showed similar adverse events except for conjunctival hyperemia (Table 3). The incidence of conjunctival hyperemia was 4/27 (14.8%) with latanoprost and 8/27 (29.6%) with tafluprost, which were not significantly

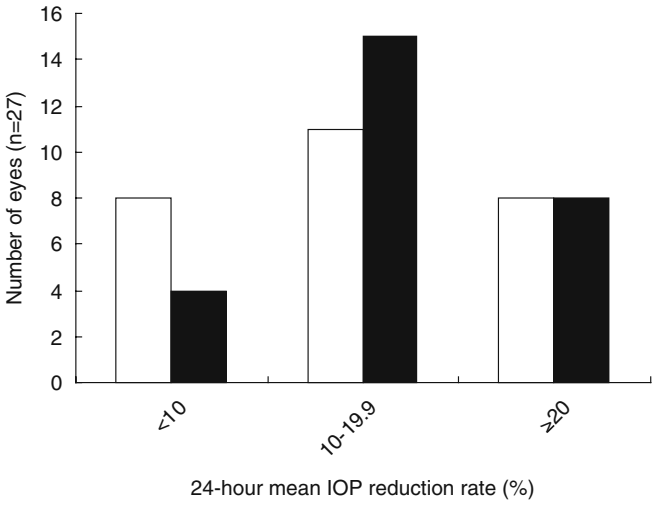

Figure 4. Histogram showing the number of subjects according to the rate of reduction in 24-hour mean IOP. □, latanoprost; ■, tafluprost. The average rate for all subjects was 16.3% for tafluprost and 15.2% for latanoprost.

Table 3. Ocular adverse events ($n = 27$)

	Latanoprost n (%)	Tafluprost n (%)
Conjunctival hyperemia	4 (14.8)	8 (29.6)
Stinging	2 (7.4)	0 (0)
Superficial punctate keratitis	2 (7.4)	2 (7.4)
Blurred vision	0 (0)	1 (3.7)

different ($P = 0.327$, Fisher's exact test). One subject reported blurred vision after administration of tafluprost, but it was mild and transient and caused no difficulties.

Discussion

The effects of tafluprost and latanoprost over a 24-h period were compared in a crossover trial that involved 27 volunteers. Both agents showed similar effects, but tafluprost was associated with a greater reduction in IOP at 24 h after administration.

There was a statistically significant difference between the two drugs in terms of the reduction in IOP from baseline, indicating that the IOP-lowering effect differed between the two drugs. Tafluprost showed a greater IOP reduction in the second half of the 24-h measurement period. When the IOP reduction was compared at each time point, tafluprost was statistically more effective than latanoprost after 24 h (7 p.m., end of the 24-h curve). According to Sutton et al.,[11] tafluprost 0.005% is more effective in IOP reduction than either latanoprost or tafluprost 0.0025%, and the dose, close to that of the market product, is more effective than latanoprost after 24 h. Similar results were found in this study. Konstas et al.[13] reported that travoprost 0.004% was more effective in reducing IOP than latanoprost at 21 h after administration. He speculated that this result was due to the affinity of travoprost for the fluoroprostaglandin (FP) F2α receptor. Tafluprost has been reported to have a 12-fold higher affinity than latanoprost to the FP receptor.[10] Thus, our results might be due to differences in FP receptor affinity.

The mean 24-h IOP reduction achieved with the two drugs was compared to determine which drug more effectively reduced IOP over 24 h; however, there were no differences between tafluprost and latanoprost. In addition, there were no differences in reductions of either IOP fluctuations or maximum IOP, which might be involved in the progression of glaucomatous visual field loss. Both agents showed similar effects in terms of the gross reduction in 24-h IOP.

In patients with low IOP and a baseline IOP of 13–15 mmHg, latanoprost,[14] bimatoprost,[15] and travoprost[16] can reduce IOP by approximately 15%. Despite the relatively short duration of administration (7 days), our results are similar to those of previous reports (tafluprost 16.3%; latanoprost 15.2%). Both medications were effective in subjects with IOP values in the low teens.

About 10% of patients with either primary open-angle glaucoma or ocular hypertension with a baseline IOP of 24 mmHg who use latanoprost show a reduction in IOP of <10%.[17] The number of subjects in this study whose 24-h reduction in IOP was <10% (about 30%) was higher than that in previous studies. This finding is probably due to the low baseline IOP of our subjects. However, our results were better than those reported by Ikeda et al.,[3] who measured the reduction in IOP elicited by latanoprost in patients with normal-tension glaucoma, and found that over 40% of subjects showed an IOP reduction of less than 10%. Because we calculated the reduction rate over 24 h, we were able to achieve better results. Calculating the rate of reduction by measuring IOP throughout a 24-h period rather than at a single time point provides a more accurate estimate of the changes in IOP.

PG agents used for more than 6 months may increase the reduction in IOP.[17] It is possible that a longer duration of administration would have increased the magnitude of IOP reduction in our study, and tafluprost might have shown a better reduction rate, even in subjects with IOP values in the low teens. The number of subjects whose 24-h IOP reduction was <10% with tafluprost was half the number with latanoprost. Meanwhile, tafluprost was effective in five of eight subjects whose IOP reduction was <10% with latanoprost, suggesting that tafluprost should be considered for patients with a poor response to latanoprost.

With the exception of conjunctival hyperemia, there was no difference in the incidence of adverse events between the two drugs used here. Latanoprost has been reported to induce conjunctival hyperemia less frequently than other PG agents.[13,18,19] Similar to a previous report,[11] this study also revealed that more subjects developed conjunctival hyperemia with tafluprost than with latanoprost, even though the concentration of tafluprost used in this study was lower than that in the earlier study. The difference in hyper-

emia, while not statistically significant, is possibly clinically significant.

This study demonstrated that when studied in healthy volunteers, tafluprost 0.0015%, a commercially available preparation, was equivalent to latanoprost 0.005% in terms of the 24-h reduction in mean IOP. Tafluprost showed a statistically greater IOP reduction after 24 h than latanoprost. Tafluprost also showed a higher rate of conjunctival hyperemia.

There are several weaknesses in the present study. The subjects in this trial were young volunteers, and the full efficacy of PG agents is not usually seen until 4–6 weeks after therapy is started. Thus, results from actual clinical use with a longer duration of therapy are needed to confirm the clinical significance of these results. In addition, this study was not a double-masked comparison. Thus, the study has a potential bias as a result of its being open-label.

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