Hiroshima J. Med. Sci.
Vol. 57, No. 2, 69~72, June, 2008
HIJM 57–9

Efficacy of Latanoprost When Stored at Room Temperature

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ABSTRACT

We compared the ocular hypotensive effect for 24 hours and the tolerability of latanoprost stored at 4°C and 30°C. Seventeen healthy volunteers were included in this crossover trial. Latanoprost 0.005% (Xalatan) was stored at 4°C or 30°C for 4 weeks in the dark. The subjects enrolled to the study were randomly assigned to receive either latanoprost stored at 4°C or that stored at 30°C. The eye drop was applied to the right eye of each subject for 3 days. The left eye served as a control without administration. Slit-lamp biomicroscopy and circadian intra ocular pressure (IOP) curve was performed at Day 3, every 3 hours from 6 pm. This procedure was repeated 7 days after changing the drug from 4°C to 30°C or vice versa, and application to the left eye for 3 days. Eyes treated with latanoprost, stored both at 4°C and 30°C, achieved statistically significantly lower mean IOPs than untreated eyes at all time points, except at 21 hours treated by the drug stored at 30°C. We subtracted the IOP of eyes receiving latanoprost from the IOP of untreated eyes for each time point to evaluate the efficacy of the eye drops (delta IOP). There were no statistically significant differences between the delta IOPs with the drug stored at 4°C and 30°C. During the study, no subject developed a serious adverse event. These results suggest that latanoprost stored at 30°C for 4 weeks after opening the bottle remains as effective and safe as latanoprost stored under cold conditions.

Key words: *Latanoprost, Xalatan, Circadian IOP, Sub-optimal storage*

Latanoprost[1], a derivative of prostaglandin F2α -isopropyl-ester that reduces intraocular pressure (IOP) significantly and causes few systemic adverse effects, is most frequently prescribed in the treatment of glaucoma and ocular hypertension. According to the manufacturer's instructions, an unopened bottle should be stored under refrigeration to stabilize the chemical structure of latanoprost, and an opened bottle may be stored at a room temperature up to 25°C for 6 weeks in the USA and Europe. The chemical stability of the product against heat has already been reported[5], but no report has been published that evaluates the efficacy of eye drops stored at sub-optimal temperature. In Japan, until recently, patients were instructed to keep latanoprost under cold conditions after opening the bottle. As this condition is inconvenient for patients using latanoprost, sub-optimal storage situations may occur during daily use.

In addition, the efficacy of eye drops should be confirmed by the circadian curve of IOP because appropriate IOP reduction including nocturnal change is necessary to treat glaucoma[4].

In the present study, we compared the ocular hypotensive effect for 24 hours and the tolerability of latanoprost stored at 4°C and 30°C.

The results of this study should provide practitioners and patients with direct information about whether the drug is still effective when stored at daily conditions for one month.

METHODS

Seventeen healthy volunteers, 14 men and 3 women, ranging in age from19 to 33 years (mean

This study has no financial connection with any organization.
Clinical trials registration reference number: UMIN000000706

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22.4 years), were included in this crossover trial. The ethics committee at Hiroshima University Graduate School of Biomedical Science approved the study protocol. Written informed consent was obtained from all subjects.

First, each subject received an ophthalmic examination, including best-corrected visual acuity, IOP using Goldmann tonometer, slit-lamp biomicroscopy, funduscopy and Humphrey field analyzer 30-2 SITA-fast program. Mean IOP was 15.60+/-1.0 mmHg in the right eye and 15.55+/-1.0mmHg in the left eye. There was no significant difference between right and left IOP (paired t-test). Subjects were excluded for any of the following reasons; 1) abnormal finding revealed by the ophthalmological examination; 2) history of ocular disease; 3) previous eye surgery; 4) suspected allergic reactions to the study drugs; or 5) inability to follow the protocol.

Latanoprost 0.005% (Xalatan) was obtained from Pfizer (Tokyo, Japan). It was stored at 4°C or 30°C for 4 weeks in the dark.

All of the subjects enrolled in the study were randomly assigned to receive latanoprost stored either at 4°C or at 30°C. The eye drop was applied to the right eye of each subject at 7:00 pm for 3 days. The left eye served as the control without administration. Slit-lamp biomicroscopy and circadian IOP curve was performed and the subjects were asked about subjective symptoms related

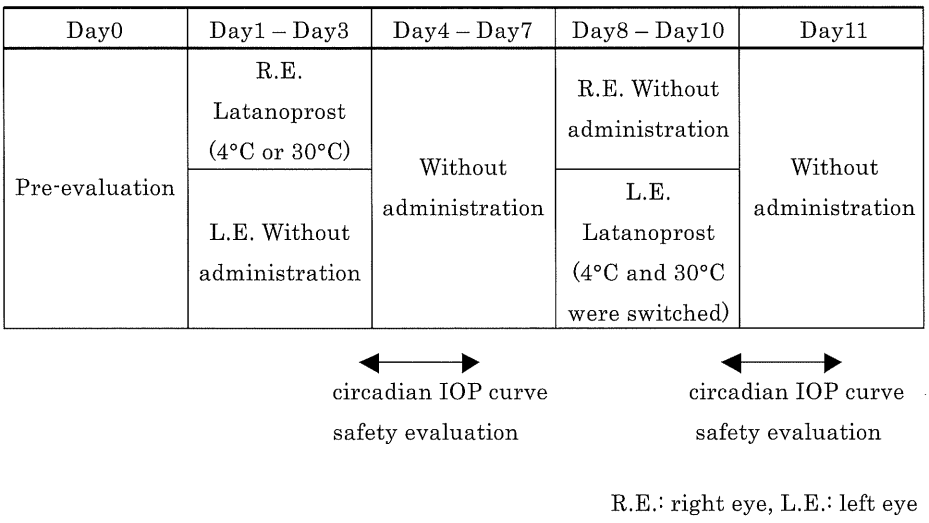

Fig. 1. Study Outline

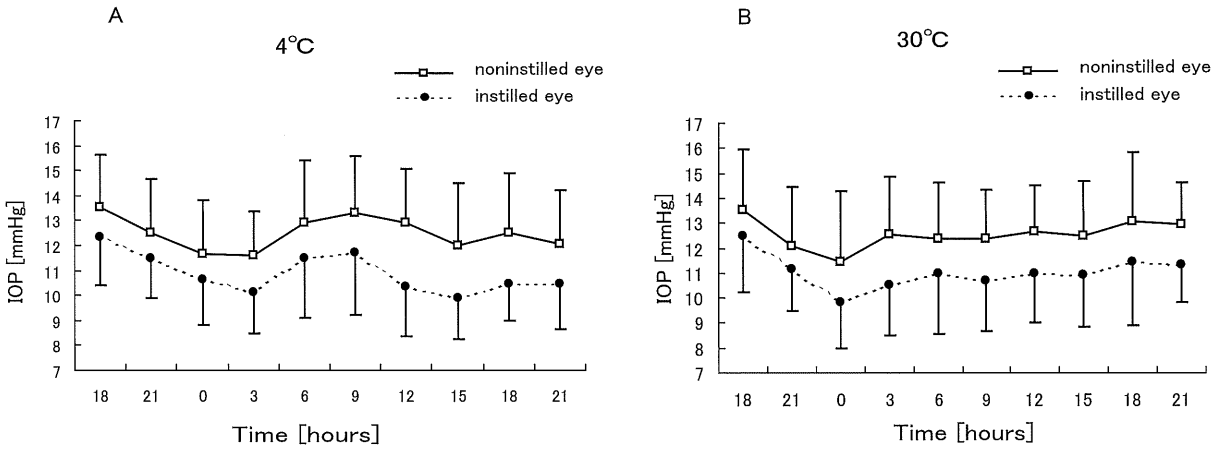

Fig. 2. The circadian mean IOP curve in each group.
Solid line: noninstilled eye. Dotted line: instilled eye.
Latanoprost, stored at both 4°C (A) and 30°C (B), achieved statistically significantly lower mean IOPs than untreated eyes at all time points, except at 21 hour treated by drug stored at 30°C (paired t-test).

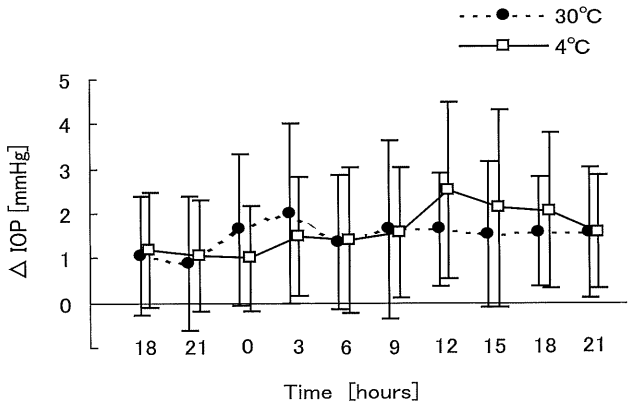

Fig. 3. The IOP of eyes receiving latanoprost was subtracted from the IOP of untreated eyes for each time point to evaluate the efficacy of the eye drops (delta IOP).
There were no statistically significant differences between the delta IOPs with the drug stored at 4°C and that of 30°C (paired t test).

to instillation by one investigator at Day 3. This procedure was repeated at Day 8 with a change to the drug stored at the opposing temperature and application to the left eye for 3 days. The right eye served as the control without administration during the second phase. The study outline is shown in Fig. 1.

IOP was measured at 6, 9 pm, midnight, 3,6,9 am, noon, 3, 6, 9 pm by the same evaluator using a calibrated single Goldmann applanation tonometer (Haag-Streit, Bern, Switzerland) with subjects sitting at the slit-lamp.

The results are given as mean +/– standard deviation. The IOPs at each time point were compared by paired t-test with one-tailed for intragroup analysis and two-tailed for difference of IOP reduction between the 4°C group and the 30°C group. A significance level $p<0.05$ was used.

RESULTS

All 17 subjects completed this study.

Figure 2 shows the circadian IOP curve in each group. Eyes treated with latanoprost stored at both 4°C (A) and 30°C (B), achieved statistically significantly lower mean IOP than untreated eyes at all time points, except at 21 hours treated with the drug stored at 30°C.

We subtracted the IOP of eyes receiving latanoprost from the IOP of untreated eyes for each time point to evaluate the IOP reduction by the eye drops (delta IOP). There were no statistically significant differences between delta IOPs with the drug stored at 4°C and those at 30°C (Table 1, Fig. 3).

During the study, no subject developed a serious adverse event or discontinued the study. The safety evaluation was based on slit-lamp biomicroscopy. Table 2 lists all adverse events. Conjunctival hyperemia was noted in 5 subjects treated with latanoprost stored at 4°C and 4 subjects treated with that stored at 30°C. All conjunctival hyperemia was at a trace level. One subject developed faint superficial punctate keratitis when treated with latanoprost stored at 4°C. No subject complained of a smarting sensation or itching.

Table 1. Delta IOP (mmHg ± SD)

Time	4°C	30°C	4°C Versus 30°C
18:00	1.18 ± 0.31	1.06 ± 0.33	P=0.81
21:00	1.06 ± 0.30	0.88 ± 0.36	P=0.65
0:00	1.00 ± 0.28	1.65 ± 0.41	P=0.084
3:00	1.47 ± 0.32	2.00 ± 0.49	P=0.37
6:00	1.41 ± 0.39	1.35 ± 0.36	P=0.91
9:00	1.59 ± 0.35	1.65 ± 0.48	P=0.93
12:00	2.53 ± 0.48	1.65 ± 0.31	P=0.15
15:00	2.12 ± 0.53	1.53 ± 0.39	P=0.23
18:00	2.06 ± 0.42	1.59 ± 0.30	P=0.26
21:00	1.59 ± 0.31	1.59 ± 0.35	

Table 2. Incidence of adverse events at Day 3 and Day 10. The safety evaluation was based on slit-lamp biomicroscopy.

	4°C (n = 17)	30°C (n = 17)
Conjunctival hyperemia	5	4
Superficial punctate keratitis	1	0
Smarting sensation or itching	0	0

DISCUSSION

Latanoprost ophthalmic solution has a storage temperature requirement of 2 to 8°C before being opened. Once opened, the bottle may be stored at room temperature in European countries and in the United States. Morgan[5] reported experimental storage in the laboratory: no measurable degradation of latanoprost occurred in the samples stored at 4 and 25°C during the study. In contrast, the storage of latanoprost at temperatures of 50 and 70°C resulted in a rapid degradation. Varma[6] collected latanoprost bottles from patients and measured the concentrations in the residual solutions. He reported that latanoprost remains stable after 4 or 6 weeks of patient use when stored at room temperature. These studies showed the chemical stability of latanoprost; however, no studies have confirmed the actual efficacy of latanoprost 0.005% ophthalmic solution stored at room temperature. In Japan until March 2007, patients were recommended to store latanoprost under refrigeration even after the bottle was opened. This instruction was inconvenient for patients prescribed the drug.

In the present study, we compared the ocular hypotensive effect of latanoprost stored at 4°C and 30°C. This is the first report that has evaluated the ocular hypotensive effect of the eye drops kept at room temperature. The analysis of IOP reduction in our study indicates that latanoprost is still effective after the bottle has been stored at 30°C for 4 weeks.

According to Hotehama[2, 3], latanoprost reduces IOP with a single administration. He reported that IOP reduction at 8 hours after an administration of 0.006% latanoprost was 2.1 mmHg for healthy volunteers, ranging in age from 18 to 35. In our study, the administration period was 3 days and maximum IOP reduction was 2.5 and 2.0 mmHg at 4°C and 30°C, respectively. There is no major discrepancy between these results.

Side effects were minimal in the present study and latanoprost stored at either temperature was well tolerated. No subjects complained of itching or burning sensation, and no new adverse events were reported. Latanoprost has been reported to induce conjunctival hyperemia. Hyperemia with either eye drops was the most common finding but it was faint and did not appear to be associated with intraocular inflammation. The effect on eyelash growth and iris pigmentation could not be detected because the administration period was short.

These results suggest that latanoprost after opening the bottle stored at 30°C for 4 weeks remains effective and as safe as latanoprost stored under cold conditions.

(Received March 4, 2008)
(Accepted May 19, 2008)

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