A double masked comparison of the intraocular pressure reducing effect of latanoprost 0.005% and 0.001% administered once daily in open angle glaucoma and ocular hypertension

Björn Friström, Sven Erik G Nilsson

Abstract

Aim—to compare the intraocular pressure (IOP) reducing effect of latanoprost 0.005% and 0.001%.

Methods—Twenty four patients with glaucoma or ocular hypertension were randomised into two groups. Twelve patients (group 1) were given latanoprost 0.005% once daily for 4 weeks and then latanoprost 0.001% once daily for the following 4 weeks. Twelve patients (group 2) were given latanoprost 0.001% once daily for 4 weeks and then latanoprost 0.005% for the following 4 weeks.

Results—There was a significant IOP reduction from baseline in both groups on day 28 as well as on day 56. When the results from both groups were used for calculations, the mean IOP reduction from baseline after 4 weeks of treatment with latanoprost 0.005% (day 28 or 56) was 9.6 (SD 3.3) mm Hg (35.0%). After 4 weeks of treatment with latanoprost 0.001%, the IOP reduction (day 28 or 56) was 7.6 (3.4) mm Hg (27.7%). The difference in IOP reduction between the two concentrations was 2.0 (2.3) mm Hg (p<0.001).

Conclusions—Latanoprost 0.005% was more effective than latanoprost 0.001% in reducing IOP. Even the lower concentrations of certain PGs, does not seem to be a clinical problem when latanoprost is given once daily at a concentration of 0.005%. However, changes in iris colour have recently been reported in some patients treated with latanoprost 0.005% given once daily for more than 3 months. Increased iris pigmentation developed in some eyes with mixed iris colour (hazel, green-brown, or blue-brown). Studies in monkeys seem to indicate that such iris pigmentation may be dose dependent (J Stjernschantz, personal communication). If so, it may be of value to test latanoprost at lower concentrations than 0.005% regarding IOP reduction as well as effects on iris pigmentation.

Patients and methods

STUDY DESIGN

The study was performed with a randomised, double masked crossover design. Twenty four patients with ocular hypertension (OH), POAG, or capsular glaucoma were allocated to treatment group 1 or 2 according to a computer generated randomisation list with block size 4 and allocation 1:1. The treatment period was 8 weeks. Twelve patients (group 1) were given latanoprost 0.005% once daily for 4 weeks and then latanoprost 0.001% once daily for the following 4 weeks. Twelve patients (group 2) were given latanoprost 0.001% once daily for 4 weeks and then latanoprost 0.005% once daily for the following 4 weeks. The study was...
approved by the ethics committee of the medical faculty of the University of Linköping (Sweden) and by the National Medical Products Agency in Sweden.

DRUGS
Latanoprost in a concentration of 0.005% (vehicle containing benzalkonium chloride 0.2 mg/ml) and 0.001% (vehicle containing benzalkonium chloride 0.1 mg/ml and sodium EDTA 0.1 mg/ml), in identical bottles was supplied by Pharmacia AB, Uppsala, Sweden. The vehicle of latanoprost was modified due to the lower concentration. No significant difference has been found with respect to the absorption of latanoprost between the two vehicles (unpublished data from Pharmacia and Upjohn).

PATIENT SELECTION
Patients above the age of 18 with unilateral or bilateral POAG, capsular glaucoma, or OH were included. OH is defined as an IOP constantly ≥23 mm Hg. Glaucoma is diagnosed when a patient has glaucomatous visual field defects and/or a glaucomatous optic disc. For patients to be eligible, an IOP of 22 mm Hg or higher had to be measured during the pre-study period. Patients on treatment for elevated IOP were eligible for inclusion after a washout period of 3 weeks for β adrenergic blockers, 2 weeks for adrenergic agonists, and 5 days for cholinergic agonists and oral carbonic anhydrase inhibitors. Exclusion criteria were history of acute angle closure, intraocular surgery or argon laser trabeculoplasty within 6 months of study start; severe dry eye syndrome; and ocular inflammation/infection within 3 months of inclusion. Twenty-four patients were included, 10 men and 14 women, with a mean age of 67.9 years (range 44–82 years). Fifteen patients fulfilled the criteria of eligibility for both eyes and nine for one eye only. One patient had POAG in both eyes and one patient POAG in one eye. All others had OH. After informed consent was obtained, patients were randomised into group 1 or group 2.

TREATMENT AND EXAMINATION SCHEDULE
The preinclusion examination for eligibility was performed within 4 weeks of the start of the study. Medical and ophthalmic histories were obtained. Measurements of IOP, slit-lamp examination, ophthalmoscopic examination of the fundus and the optic nerve head, and gonioscopy were performed. The visual field was examined (Humphrey 24-2) at preinclusion day if not examined within the past 6 months.

The treatment period of 8 weeks included three visits; day 1 (baseline), day 28, and day 56. On those days, the IOP was measured at 8 am, noon and 4 pm. Each IOP measurement was the mean of three consecutive readings. At each visit, slit-lamp examination was performed. On day 56, a full ophthalmic examination, including visual fields, was performed.

Fifteen patients who fulfilled the criteria of eligibility for both eyes were treated in both eyes and nine patients with unilateral disease were treated in the affected eye only. The patients were instructed to take the latanoprost eye drops in the evening at approximately 8 pm (7–9 pm) throughout the study period. The first drop was administered in the evening of day 1 (baseline day) and the last one in the evening of day 55. On day 28, the treatment was changed between the groups without washout in between. The patients were instructed carefully by the investigator on how and when to apply their medication. The day before a visit, an assistant phoned each patient reminding them to administer the eye drops. In the morning of each visit, the investigator asked the patient to state when the last eye drops were administered. No other topical medication known to affect IOP was used during the study. Patients who during the study initiated or changed systemic medication known to affect IOP were withdrawn.

All calculations and statistical analysis were based on the diurnal IOP. The diurnal IOP was defined as the mean value of the IOP readings obtained at 8 am, noon, and 4 pm.

Table 1 Reductions in diurnal intraocular pressure (IOP) from baseline in groups 1 and 2

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
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<tbody>
<tr>
<td><strong>Group 1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1 (baseline)</td>
<td>27.9 (3.5)</td>
<td>35.9–24.1</td>
</tr>
<tr>
<td>Day 28</td>
<td>19.5 (2.6)</td>
<td>24.4–14.4</td>
</tr>
<tr>
<td>Reduction in IOP (mm Hg) (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1–day 56</td>
<td>–9.4 (4.1)</td>
<td>–16.9 to –4.3</td>
</tr>
<tr>
<td>Day 28–day 56</td>
<td>0.8 (1.6)</td>
<td>–1.1 to +3.7</td>
</tr>
<tr>
<td><strong>Group 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1 (baseline)</td>
<td>26.8 (2.3)</td>
<td>31.9–23.9</td>
</tr>
<tr>
<td>Day 28</td>
<td>19.9 (2.6)</td>
<td>24.8–15.8</td>
</tr>
<tr>
<td>Reduction in IOP (mm Hg) (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1–day 56</td>
<td>–9.2 (3.8)</td>
<td>–17.2 to +3.9</td>
</tr>
<tr>
<td>Day 28–day 56</td>
<td>–0.9 (1.6)</td>
<td>–1.1 to +3.7</td>
</tr>
</tbody>
</table>

Mean of measurements 8 am, noon, and 4 pm. If both eyes were included, the mean of both eyes was used in calculations.

*p<0.001, †p<0.0001, ns = not significant (paired t test).
Comparison of the IOP reducing effect of latanoprost in open angle glaucoma and ocular hypertension

Results
Twenty four patients (all included) completed the study. One patient (group 1), who was treated for coronary heart disease with an oral \( \beta \) blocker medication on day 1, stopped that medication during the second treatment period on order by her general practitioner. The patient had recovered and there was no longer any need for the medication. According to the protocol, the IOP values from this patient are not included in calculations or figures. Table 1 and Figure 1 present the mean IOPs of the treatment groups obtained on day 1, day 28, and day 56. There was a significant IOP reduction in both groups. In group 1, the IOP reduction on day 28 (latanoprost 0.005%) was 9.2 mm Hg (\( p<0.0001 \)) and on day 56 (latanoprost 0.001%) 8.4 mm Hg (\( p<0.0001 \)). In group 2, the IOP reduction on day 28 (latanoprost 0.001%) was 6.9 mm Hg (\( p<0.0001 \)) and on day 56 (latanoprost 0.005%) 9.9 mm Hg (\( p<0.0001 \)). The difference in IOP reduction in group 1 between day 28 and day 56 was 0.8 mm Hg (\( p>0.05 \)). The difference in IOP reduction in group 2 between day 28 and day 56 was 3.0 mm Hg (\( p<0.0001 \)). The percentage change in IOP in group 1 on days 28 and 56 compared with baseline was 33.0% and 30.1%, respectively. In group 2, the corresponding change was 25.7% and 36.9%, respectively. When the results from both groups are used for calculations (Table 2), the mean IOP reduction after 4 weeks of treatment with latanoprost 0.005% (day 28 or 56) was 9.6 mm Hg (35.0%) and after 4 weeks of treatment with latanoprost 0.001% (day 28 or 56) 7.6 mm Hg (27.7%). Thus, the difference in IOP reduction between the two concentrations was 2.0 mm Hg (\( p<0.001 \)). There was a difference in response between the two treatment periods. The IOP reduction was more effective during the second period. The difference in IOP reduction between the two periods was 1.1 mm Hg (\( p = 0.01 \), ANOVA). Figure 2 shows the IOP reduction at 8 am, at noon, and at 4 pm on days 1, 28, and 56. The reduction appears to be well maintained throughout the day. There were no changes in the visual fields for any of the patients during the study period. The three glaucomatous eyes did not differ from those with ocular hypertension in response to the two concentrations of latanoprost.

Table 2  Reduction in diurnal intraocular pressure (IOP) for all patients (\( n=22 \)), treated with latanoprost 0.005% or 0.001% given once daily

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
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<tbody>
<tr>
<td>Baseline (day 1)</td>
<td>27.4 (2.9)</td>
</tr>
<tr>
<td>0.001% (day 28 or 56)</td>
<td>19.7 (2.5)</td>
</tr>
<tr>
<td>0.005% (day 28 or 56)</td>
<td>17.8 (2.2)</td>
</tr>
<tr>
<td>Reduction in diurnal IOP (mm Hg)</td>
<td></td>
</tr>
<tr>
<td>0.001% (day 1–day 28 or 56)</td>
<td>-7.6 (3.4) (27.7%)</td>
</tr>
<tr>
<td>0.005% (day 1–day 28 or 56)</td>
<td>-9.6 (3.3) (35.0%)</td>
</tr>
<tr>
<td>Lat 0.005%–Lat 0.001%</td>
<td>2.0 (2.4)*</td>
</tr>
</tbody>
</table>

SID EFFECTS
There were very few and only mild ocular side effects. Three patients in group 1 and one patient in group 2 sensed a slight burning in the eye after administering the eyedrops on day

Figure 2  Reduction in intraocular pressure (IOP) from baseline (day 1) by time of day on days 28 and 56. Group 1, treatment with latanoprost 0.005% once daily at 8 pm from day 1 to day 27 and with latanoprost 0.001% once daily at 8 pm from day 28 to day 55. Group 2, treatment with latanoprost 0.001% once daily at 8 pm from day 1 to day 27 and with latanoprost 0.005% once daily at 8 pm from day 28 to day 55.
(group 1, day 56), respectively. Thus, the higher concentration of latanoprost was more effective. The mean difference in IOP reduction between the two concentrations was found to be 2.0 mm Hg. From a clinical point of view, the IOP reducing effect appears to be well maintained throughout the day for both concentrations (Fig 2). There was no large difference between IOP at 8 am (12 hours after treatment) and 4 pm (20 hours after treatment).

There was a difference in response between the two treatment periods (Fig 1, Table 1). The IOP reducing effect was 1.1 mm Hg more effective for the second treatment period. It is not likely that this difference was induced by a true carryover from the first treatment period. Both groups show a better response during the second treatment period and it is not likely to have a carryover effect from the lower concentration to the higher. The ANOVA test of the carryover effect shows no significance (p = 0.46), but because of the study design (2 by 2 crossover design without washout period) the carryover test suffers from a very low power. In the large studies of latanoprost 0.005% administered once daily there seems to be very little change in effect after 2 weeks of treatment.11,12 We do not know if this is true for the lower concentration. The effect of latanoprost 0.001% may possibly increase with time, which could to some extent explain the better effect during the second treatment period.

In six of the patients (group 1, four patients; group 2, two patients), the IOP reduction after 4 weeks of treatment was somewhat more pronounced for the lower concentration. In 17 patients the higher concentration was more effective, whereas in two patients the difference was <0.4 mm Hg. Thus, one third of our patients would not have obtained more clinical benefit from the higher concentration of latanoprost. In our study, patients who responded extremely well to one concentration did so also to the other concentration. The best responder to the higher concentration was also the best responder to the lower concentration. For this patient, who had OH, the IOP was 2.0 mm Hg after 4 weeks on latanoprost 0.001% and to 18.7 mm Hg after 4 weeks on latanoprost 0.005%.

Thus, although in the present study, latanoprost 0.005% was more effective than latanoprost 0.001% in reducing IOP, even the lower concentration seems to be sufficiently effective for achieving clinically ‘acceptable’ IOP control in many patients. The increase in iris pigmentation, which has recently been reported as a side effect of latanoprost 0.005% in certain patients, may be dose dependent. If so, a concentration of latanoprost as low as 0.001% may possibly reduce the risk of such a pigmentation. However, additional long term studies with a larger number of patients treated with latanoprost 0.001% should be performed to test this hypothesis.

The latanoprost eyedrops were supplied by Pharmacia AB. The investigation was supported by an unrestricted grant from Pharmacia AB.

11 Torres CB, Camras CB, Yabloniski ME. Effects of PhXAX4, a new prostaglandin F2α analog, on aqueous humor dynamics in human eyes. Ophthalmology 1993;100:1297–304.
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