

# 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 concentration was surprisingly effective, and potentially may be of importance for use in clinical practice. Furthermore, it is at present unknown whether the increase in iris pigmentation seen in certain patients treated with latanoprost 0.005% is dose dependent and might be less pronounced with latanoprost 0.001%. Long term studies with a larger number of patients are required in order to answer this question. (*Br J Ophthalmol* 1997;81:867-870)

The prostaglandin (PG) analogue latanoprost (PhXA41) and its epimeric mixture PhXA34 have been shown to reduce intraocular pressure (IOP) effectively in normal, ocular hypertensive and glaucomatous eyes.<sup>1-8</sup> Latanoprost is a selective FP receptor (PGF<sub>2α</sub>) agonist. The main mode of action of PGF<sub>2α</sub> and latanoprost is an increase in uveoscleral outflow of aqueous humour.<sup>9-10</sup> No significant effect on aqueous humour production has been found.<sup>11-12</sup>

Alm *et al* found no clear dose response relation for the IOP reducing effect of latanoprost

when tested at concentrations of 35 µg/ml, 60 µg/ml, and 115 µg/ml when given twice daily for 1 month to patients with primary open angle glaucoma (POAG), capsular glaucoma, or ocular hypertension. The variation in IOP response was, however, largest at the lowest concentration.<sup>5</sup> Racz *et al* found the duration of action of latanoprost to be more than 24 hours.<sup>6</sup> Administration of latanoprost 0.006% once daily was found to be at least as effective and apparently superior to the twice daily dose regimen.<sup>7-8</sup> This raises the question of whether it is possible to further reduce the concentration of latanoprost and still obtain a clinically useful IOP reducing effect, as discussed also by Camras in his published comment following the paper by Alm *et al*.<sup>5</sup>

Conjunctival hyperaemia, which is observed as a side effect of certain PGs, does not seem to be a clinical problem when latanoprost is given once daily at a concentration of 0.005%.<sup>13-15</sup> 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).<sup>13-15</sup> 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. The present study was designed to compare the IOP reducing effect of latanoprost 0.005% and 0.001%, respectively, administered once daily.

## 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

Department of  
Ophthalmology,  
University of  
Linköping, Linköping,  
Sweden  
B Friström  
S E G Nilsson

Correspondence to:  
Dr B Friström.

Accepted for publication  
26 March 1997

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  $\geq 23$  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  $\beta$  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 pre-inclusion 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 eyedrops 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 eyedrops. In the morning of each visit, the investigator asked the patient to state when the last eyedrops 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

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

**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 (n=11)

	Mean (SD)	Range
Day 1 (baseline)	27.9 (3.5)	35.9–24.1
Day 28 (0.005%)	18.7 (2.1)	22.1–15.2
Day 56 (0.001%)	19.5 (2.6)	24.4–14.4
Reduction in IOP (mm Hg) (%)		
Day 1–day 28	–9.2 (3.8)† (–33.0)	–17.2 to –3.9
Day 1–day 56	–8.4 (4.1)† (–30.1)	–16.9 to –4.3
Day 28–day 56	+0.8 (1.6)ns (+4.3)	–1.1 to +3.7

**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 (n=12)

	Mean (SD)	Range
Day 1 (baseline)	26.8 (2.3)	31.9–23.9
Day 28 (0.001%)	19.9 (2.6)	24.8–15.8
Day 56 (0.005%)	16.9 (2.1)	18.8–12.3
Reduction in IOP (mm Hg) (%)		
Day 1–day 28	–6.9 (2.7)† (–25.7)	–11.1 to –1.0
Day 1–day 56	–9.9 (2.8)† (–36.9)	–15.2 to –6.3
Day 28–day 56	–3.0 (2.3)* (–15.1)	–7.2 to +0.7

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).

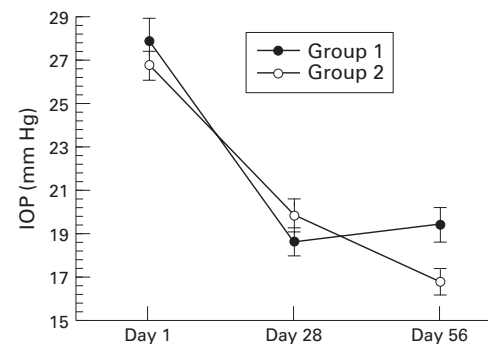


Figure 1 Reduction in intraocular pressure (IOP) from baseline (day 1) on days 28 and 56. Group 1, treatment with latanoprost 0.005% once daily at 8 pm from day 1 to day 27 and with latanoprost 0.001% once daily at 8 pm from day 28 to day 55. Group 2, treatment with latanoprost 0.001% once daily at 8 pm from day 1 to day 27 and with latanoprost 0.005% once daily at 8 pm from day 28 to day 55. The values are mean of measurements at 8 am, noon, and 4 pm. Error bars indicate standard error.

obtained at 8 am, noon, and 4 pm for the eligible eye(s) of each patient. The data were analysed with an analysis of variance for 2 by 2 crossover design with group, patient within group, period and treatment factors, and diurnal IOP as response (ANOVA). Further, Student's paired *t* test (two tailed) was performed separately for each group on the difference in diurnal IOP reduction between the two treatments.

### 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 ( $p < 0.001$ ). 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.

### SIDE 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

Table 2 Reduction in diurnal intraocular pressure (IOP) for all patients ( $n=23$ ), treated with latanoprost 0.005% or 0.001% given once daily

	Mean (SD)
Baseline (day 1)	27.4 (2.9)
0.001% (day 28 or 56)	19.7 (2.5)
0.005% (day 28 or 56)	17.8 (2.2)
Reduction in diurnal IOP (mm Hg)	
0.001% (day 1–day 28 or 56)	-7.6 (3.4) (27.7%)
0.005% (day 1–day 28 or 56)	-9.6 (3.3) (35.0%)
Lat 0.005%–Lat 0.001%	2.0 (2.3)*

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

\* $p < 0.001$ , ANOVA.

28. This sensation disappeared after a few days, despite continuing treatment. None of these patients showed any conjunctival hyperaemia on day 56. It is not likely that the reduction in concentration of latanoprost on day 28 for the three patients in group 1 could have caused the burning sensation. The difference in vehicle may possibly be the explanation for all four patients.

### Discussion

The objective of this study was to compare the IOP reducing effect of latanoprost 0.005% and 0.001%. The effect of latanoprost 0.005% is well known from three recent large scale clinical trials comparing the IOP reducing effect of latanoprost 0.005% and timolol 0.5%.<sup>13–15</sup> The effect of latanoprost on diurnal IOP was found to be superior to that of timolol in two of these studies<sup>13 15</sup> and at least as good as timolol in the third study.<sup>14</sup> The IOP reducing effect of latanoprost 0.005% administered once daily in these three studies ranged from 27% to 35%.

In our study, the IOP reduction after 4 weeks of treatment with latanoprost 0.005% was 33.0% (group 1, day 28) and 36.9% (group 2, day 56), respectively. After 4 weeks of treatment with latanoprost 0.001%, the IOP reduction was 25.7% (group 2, day 28) and 30.1%

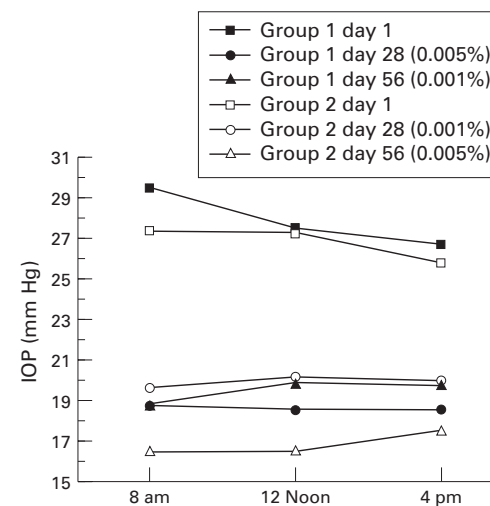


Figure 2 Reduction in intraocular pressure (IOP) from baseline (day 1) by time of day on days 28 and 56. Group 1, treatment with latanoprost 0.005% once daily at 8 pm from day 1 to day 27 and with latanoprost 0.001% once daily at 8 pm from day 28 to day 55. Group 2, treatment with latanoprost 0.001% 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.<sup>13-15</sup> 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 reduced from 35.9 mm Hg (baseline) to 19.0 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 con-

trol 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.

- Alm A, Villumsen J. PhXA34, a new potent ocular hypotensive drug. A study on dose-response relationship and on aqueous humor dynamics in healthy volunteers. *Arch Ophthalmol* 1991;109:1564-8.
- Villumsen J, Alm A. PhXA34—a prostaglandin  $F_{2\alpha}$  analogue. Effect on intraocular pressure in patients with ocular hypertension. *Br J Ophthalmol* 1992;76:214-7.
- Camras CB, Schumer RA, Marsk A, Lustgarten JS, Serle JB, Stjernschantz J, et al. Intraocular pressure reduction with PhXA34, a new prostaglandin analogue, in patients with ocular hypertension. *Arch Ophthalmol* 1992;110:1733-8.
- Frström B, Nilsson SEG. Interaction of PhXA41, a new prostaglandin analogue, with pilocarpine. A study on patients with elevated intraocular pressure. *Arch Ophthalmol* 1993;111:662-5.
- Alm A, Villumsen J, Törnquist P, Mandahl A, Airaksinen J, Tuulane A, et al. Intraocular pressure-reducing effects of PhXA41 in patients with increased eye pressure. A one-month study. *Ophthalmology* 1993;100:1312-7.
- Racz P, Ruzsonyi MR, Nagy ZI, Bito LZ. Maintained intraocular pressure reduction with once-a-day application of a new prostaglandin  $F_{2\alpha}$  analogue (PhXA41). An in-hospital, placebo-controlled study. *Arch Ophthalmol* 1993;111:1351-8.
- Nagasubramanian S, Sheth GP, Hitchings RA, Stjernschantz J. Intraocular pressure-reducing effect of PhXA41 in ocular hypertension. Comparison of dose regimens. *Ophthalmology* 1993;100:1305-11.
- Alm A, Widengård I, Kjellgren D, Soderstrom M, Fristrom B, Heijl A, et al. Latanoprost administered once daily causes a maintained reduction of intraocular pressure in glaucoma patients treated concomitantly with timolol. *Br J Ophthalmol* 1995;79:12-6.
- Gabelt BT, Kaufman PL. Prostaglandin  $F_{2\alpha}$  increases uveoscleral outflow in the cynomolgus monkey. *Exp Eye Res* 1989;49:389-402.
- Nilsson SFE, Samuelsson M, Bill A, Stjernschantz J. Increased uveoscleral outflow as a possible mechanism of ocular hypotension caused by prostaglandin  $F_{2\alpha}$ -1-isopropylester in the cynomolgus monkey. *Exp Eye Res* 1989;48:707-16.
- Toris CB, Camras CB, Yablonski ME. Effects of PhXA41, a new prostaglandin  $F_{2\alpha}$  analog, on aqueous humor dynamics in human eyes. *Ophthalmology* 1993;100:1297-304.
- Ziai N, Dolan JW, Kacere RD, Brubaker RF. The effects on aqueous dynamics of PhXA41, a new prostaglandin  $F_{2\alpha}$  analogue, after topical application in normal and ocular hypertensive human eyes. *Arch Ophthalmol* 1993;111:1351-8.
- Camras CB, the United States Latanoprost Study Group. Comparison of latanoprost and timolol in patients with ocular hypertension and glaucoma. A six-month, masked, multicenter trial in the United States. *Ophthalmology* 1996;103:138-47.
- Watson P, Stjernschantz J, the Latanoprost Study Group. A six-month, randomized, double-masked study comparing latanoprost with timolol in open-angle glaucoma and ocular hypertension. *Ophthalmology* 1996;103:126-37.
- Alm A, Stjernschantz J, the Scandinavian Latanoprost Study Group. Effects on intraocular pressure and side effects of 0.005% latanoprost applied once daily, evening or morning. A comparison with timolol. *Ophthalmology* 1995;102:1743-52.



## 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 and Sven Erik G Nilsson

*Br J Ophthalmol* 1997 81: 867-870

doi: 10.1136/bjo.81.10.867

---

Updated information and services can be found at:

<http://bjo.bmj.com/content/81/10/867.full.html>

---

*These include:*

### References

This article cites 14 articles, 6 of which can be accessed free at:

<http://bjo.bmj.com/content/81/10/867.full.html#ref-list-1>

Article cited in:

<http://bjo.bmj.com/content/81/10/867.full.html#related-urls>

### Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

---

### Topic Collections

Articles on similar topics can be found in the following collections

[Angle](#) (791 articles)

[Intraocular pressure](#) (789 articles)

[Glaucoma](#) (779 articles)

---

### Notes

---

To request permissions go to:

<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:

<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:

<http://group.bmj.com/subscribe/>