Latanoprost administered once daily caused a maintained reduction of intraocular pressure in glaucoma patients treated concomitantly with timolol

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Abstract

The long term effects of two dose regimens of latanoprost (PhXA41) administered to eyes concomitantly treated with timolol which had not adequately been controlled by timolol alone were compared. A total of 50 patients, 17 with primary open angle glaucoma and 33 with capsular glaucoma, were recruited from five clinics. All had glaucomatous visual field defects and an intraocular pressure (IOP) of at least 22 mm Hg despite treatment with 0.5% timolol twice daily. Patients were randomised to two treatment groups. In one group 0.006% latanoprost was given twice daily, in the other group placebo was given at 8 am and latanoprost at 8 pm for 3 months, with concomitant timolol treatment in both groups. Average daytime IOP (mean (SD)) at baseline (on timolol alone) and after 4 and 12 weeks' treatment was 24.8 (3.6), 16.8 (4.3), and 15.7 (2.4) mm Hg respectively with once daily application of latanoprost and 24.9 (2.9), 18.1 (3.0), and 18.0 (3.6) mm Hg respectively with latanoprost twice daily. No clinically significant side effects were observed during treatment. Latanoprost causes a marked and sustained IOP reduction in eyes which are also being treated with timolol. Latanoprost given once daily is at least as effective and probably superior to a twice daily dose regimen

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In a first dose finding study with twice daily administrations of latanoprost, ocular hypertensive eyes were treated for 4 weeks.⁵ There was no significant difference between the three concentrations of latanoprost eye drops used; 0.0035%, 0.006%, and 0.0115%, and all were significantly better than placebo. The initial response, on the second day of treatment, was good with a 31-38% reduction of the IOP, but after 1 week of treatment there was some diminution of effect and after 4 weeks the IOP reduction was between 19 and 22% for the three concentrations of latanoprost used. A partial diminution in the IOP effect was also observed by Camras *et al* after 5 days of treatment twice daily with 0.01% latanoprost, but not with 0.003%.³ Friström and Nilsson also noted some reduction of the IOP effect with 0.006% latanoprost given twice daily for 1 week, similar to that observed for 2% pilocarpine administered three times daily.⁹ They also found that the effect on IOP of latanoprost and pilocarpine was at least partially additive.⁹ Both drugs act on outflow; latanoprost has no effect on aqueous flow.¹⁶⁸ Thus one would expect latanoprost and an aqueous flow suppressor to be a better combination. The effect on IOP of prostaglandin F_{2α}-isopropylester (PGF_{2α}-IE) has previously been found to be additive to that of timolol^{10 11} and a direct comparison of the additivity of latanoprost to timolol 0.5% twice daily and pilocarpine 2% three times daily suggested that pretreatment with pilocarpine reduced the effect of latanoprost on IOP.¹²

The present study was designed to evaluate the effect of latanoprost administered either once or twice daily in addition to timolol. Treatment was given for 3 months to be able to detect any long term diminution in the effect of the drug on IOP.

Patients and methods

SUBJECT SELECTION

The study was performed as a five centre, randomised, parallel, double masked study of latanoprost, 0.006%, given either once, in the evening, or twice daily for 12 weeks. Patients of either sex over the age of 60, with primary open angle glaucoma (POAG) or capsular glaucoma, in whom the IOP was not adequately controlled despite 0.5% timolol twice daily were included. Inadequate IOP control was defined as an IOP of at least 22 mm Hg on two occasions taken at an interval of at least 1 hour at the pre-inclusion examination. Ten patients were recruited from each centre, five per treatment group. Patients

Several previous studies have demonstrated that the phenyl substituted prostaglandin F_{2α} analogue, 13,14-dihydro-17-phenyl-18,19,20-trinor-prostaglandin F_{2α}-isopropylester (latanoprost, PhXA41) and its epimeric mixture PhXA34 reduce significantly the intraocular pressure (IOP) in normal, ocular hypertensive, or glaucomatous eyes.¹⁻⁸ The present study was undertaken to obtain more information on dose regimen, long term effect, and additivity to a β adrenergic antagonist, timolol.

Latanoprost has a long duration of effect on IOP, but whether it should be administered once or twice daily is unclear. In two dose finding studies with the epimeric mixture PhXA34 a duration of at least 24 hours was observed but the effect 24 hours after the dose was less pronounced than that seen at 12 hours after the dose.¹² Such an attenuation of the effect was not observed in a study on hospitalised patients treated with latanoprost,⁷ and in one dose regimen study administration of 0.006% latanoprost once daily was at least as effective as twice daily.⁴

Table 1 Examination schedule

Investigational event	Pre-inclusion within 1 month	Day 0			Day 14	Day 28			Week 6 4 pm	Week 8 4 pm	Week 10 4 pm	Week 12		
		8	12	4	4	8	12	4				8	12	4
Ocular examination	*												*	
Symptomatology	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Visual acuity	*	*				*						*		
Biomicroscopy	*	*	*	*	*	*	*	*	*	*	*	*	*	*
Photography				*	*		*	*	*	*	*			*
Hyperaemia grading	*	*	*	*	*	*	*	*	*	*	*			*
IOP	*	*	*	*	*	*	*	*	*	*	*			*

with a history of severe ocular trauma, severe ocular inflammation within the past 3 months, or intraocular surgery within the last 6 months were excluded. Exclusion criteria also included known contraindications to β adrenergic blockers, a history of acute angle closure glaucoma, a history of significant dry eyes, and wearing contact lenses. The study protocols were reviewed and approved by the National Board of Health and Welfare and by the appropriate local review boards. Written informed consent was obtained from all subjects.

EXAMINATION SCHEDULE AND PROCEDURES

A pre-inclusion examination was performed within 1 month before the study. We obtained a medical and ophthalmic history including information on ocular symptoms. In addition to IOP determinations the initial examination included measurement of refractive error and Snellen visual acuity, a slit-lamp evaluation of the anterior segment, ophthalmoscopic examination of the optic nerve, and a visual field if one had not been performed within the last 6 months.

The examination schedule is presented in Table 1. The patients visited the clinic three times on the baseline day and 4 and 12 weeks after initiation of treatment but only once daily for examinations after 2, 6, 8, and 10 weeks' treatment. The degree of conjunctival hyperaemia was graded in the treated eye by comparison with four standard photographs corresponding to no hyperaemia, mild, moderate, and severe hyperaemia respectively. A photograph was taken of the anterior segment of the eye which was later evaluated in a masked manner.

The patients were randomised to two treatment groups. Each patient was provided with one bottle of 0.5% timolol (Blocadren, MSD) and two identical bottles, one labelled morning and one evening. For group A both bottles contained 0.006% latanoprost, for group B the morning bottle contained vehicle and the evening bottle 0.006% latanoprost. Timolol was always administered first with 5 minutes between eye drops. The first dose of latanoprost or vehicle was given in the evening, about 8 pm, of the baseline day (day 0). Patients were instructed to administer the drops in the morning at 8 am and in the evening at 8 pm throughout the study. Twenty patients were treated with timolol in both eyes before entering the study. These patients continued with timolol treatment in the fellow eye also during the study.

One patient had been on timolol for only 2 weeks before entering the study, six patients between 1 and 4 months, and the remaining 43 patients, at least 6 months.

STATISTICAL ANALYSIS AND EVALUATION OF EFFECT

Diurnal IOP was defined as the mean IOP over the day based on the values obtained at 8 am, 12 noon, and 4 pm. Owing to differences in baseline IOP between patients, baseline IOP was used as a covariate in statistical analysis of the IOP reduction. The difference in IOP reduction between treatment groups at week 12 at 4 pm was analysed by two way analysis of covariance with treatment group and centre as factors and baseline IOP as covariate. Maximal hyperaemia was defined as the highest score from the three measurements during the day. Change in maximal hyperaemia at week 12 within treatment groups was tested with the sign test. Comparison of change in maximal hyperaemia at week 12 between treatment groups was performed with Wilcoxon rank sum test. The χ^2 test was used to compare the number of patients who responded positively to latanoprost in the two groups.

Results

Of the 50 patients who entered 48 were able to complete the study. The two patients who withdrew were in the group which administered latanoprost once daily. One patient developed a keratitis after 4 weeks' treatment and one withdrew after 6 weeks and 4 days' treatment owing to difficulties in distinguishing between the dropper bottles.

Oral β blocking agents were used by one patient in the twice daily group compared with seven patients in the once daily group. Otherwise there were no major differences between treatment groups with respect to demographic or clinical data (Table 2).

The mean diurnal IOPs at baseline and weeks 4 and 12 for the two groups are presented in Table 3, and the IOPs measured at 4 pm at baseline and at 2 week intervals for 12 weeks are shown in Figure 1. After 4 weeks' treatment the mean diurnal IOP was reduced by 8.0 mm Hg in

Table 2 Demographic and clinical characteristics

	Once daily	Twice daily	All
Age			
Mean	74.0	72.6	73.3
Range	60-84	63-87	60-87
Sex (M/F)	6/19	9/16	15/35
Iris colour			
Blue/green	21	20	41
Brown	3	1	4
Grey	1	4	5
Diagnosis			
POAG	8	9	17
Capsular glaucoma	17	16	33
Family history of OH or glaucoma	11	8	19
Use of oral β blockers	1	7	8

POAG=primary open angle glaucoma.
OH=ocular hypertension.

Table 3 Mean (SD) diurnal IOP (mm Hg) at baseline, week 4, and week 12

Treatment	Baseline	Week 4	Week 12
Once daily	24.8 (3.6)	16.8 (4.3)	15.7 (2.4)
Twice daily	24.9 (2.9)	18.1 (3.0)	18.0 (3.6)
p Values for test between treatments		0.15	<0.01

the once daily group and by 6.8 mm Hg in the twice daily group which corresponds to 32 and 27% of baseline diurnal IOP, respectively. After 12 weeks' treatment the corresponding figures were 9.1 mm Hg (37%) and 6.9 mm Hg (28%) respectively, with a statistically significant difference in IOP between the two groups ($p < 0.01$).

A post hoc analysis was made to compare the clinical efficiency of the two dose regimens. Thus patients were judged to show a good response to latanoprost if they fulfilled one or both of the following definitions: (1) No recorded IOP over 21 mm Hg for any of the 10 IOP measurements during treatment in the follow up. (2) An IOP reduction of at least 15% compared with baseline on all 10 examinations during treatment.

In the once daily group 23 of 25 patients never had an IOP measurement over 21 mm Hg compared with only 10 of 25 patients in the twice daily group. This difference was statistically significant ($p = 0.0001$, χ^2). Of 25 patients treated with latanoprost once daily 21 had an IOP reduction of at least 15% on all subsequent IOP determinations compared with only eight of 25 in the twice daily group ($p = 0.0002$, χ^2).

A slight but statistically significant contralateral IOP reduction was recorded in the eyes which had not been treated with latanoprost. Comparison of the 4 pm values at baseline and week 12 revealed a 0.7 mm Hg IOP reduction from a baseline value of 18.7 mm Hg in the once daily group ($p = 0.04$) and a 1.1 mm Hg IOP reduction from a baseline of 19.8 mm Hg ($p = 0.03$) in the twice daily group. An analysis of the IOP change in the subgroups of patients treated with timolol also in the contralateral eye showed for corresponding time points a change from 18.5 to 17.8 mm Hg in the once daily group ($n = 12$) and from 21.3 to 19.8 mm Hg in the twice daily group ($n = 8$). These changes were not statistically significant.

The maximal grades of hyperaemia observed

Figure 1 Mean intraocular pressure (IOP) (SEM) at 4 pm on baseline and at 2 week intervals during treatment for 12 weeks. Both groups received 0.5% timolol twice daily at baseline and throughout the study. After the baseline measurements 0.006% latanoprost was added once daily (■) or twice daily (▲).

Figure 2 Maximum hyperaemia scores on baseline day and after 4 and 12 weeks' on 0.006% latanoprost once daily (■) or twice daily (▲). (Means (SEM).)

during the study are presented in Figure 2. A slight trend towards increased hyperaemia in latanoprost treated eyes was observed but the average hyperaemia after 4 and 12 weeks of treatment was between none and mild in both groups. Individual variations were seen but no patient discontinued the study because of unacceptable hyperaemia. At baseline four of 25 in each group had a conjunctival injection graded as at least a mild hyperaemia. After 4 and 12 weeks of treatment this increased to seven to eight patients per group, but there was no increase in the number of patients judged to have at least a moderate hyperaemia. Two such patients were seen in the once daily group at baseline but in this group all patients were judged to have less than moderate hyperaemia after 4 and 12 weeks' treatment. In the twice daily group there was one patient with moderate hyperaemia at baseline and two patients with moderate to severe hyperaemia after 4 and 12 weeks' treatment.

In the once daily group there was one report of a mild stiffness in the study eye at baseline and one report of moderate foreign body sensation in the study eye after 4 weeks' treatment. In the twice daily group mild ocular symptoms were recorded for one eye at baseline, two eyes after 2 and 4 weeks' treatment respectively, and in one eye after 8 weeks' treatment. Mild ocular symptoms in both eyes or the fellow eye only were reported by between one and four of the 50 patients on the various examination days.

No flare was seen in any patient on any examination apart from fluorescein flare after IOP measurements. On three occasions in three different patients one cell was observed in the anterior chamber, two patients at the baseline examination and one on once daily latanoprost for 10 weeks. Photographs of the anterior segment were taken for documentation of iris colour because studies on cynomolgus monkeys have shown increased iris pigmentation with long term treatment (unpublished observation). Masked observation of the photographs of the anterior segment revealed no changes in iris pigmentation throughout the study. There were no changes in visual acuity or refraction.

Discussion

This study was designed to compare two dose regimens of latanoprost administered in addition

to timolol. Latanoprost was given to patients with inadequate IOP control, and thus placebo was not used and timolol was not washed out before adding latanoprost. Most patients had been on timolol for at least 6 months and some were taking oral β blockers. Consequently, the effect on IOP of timolol alone at the start of the study is not known. Comparison of the two dose regimens can be made but it is not possible to calculate the combined effect of the two drugs. The results, however, are clear; latanoprost causes a marked and significant reduction of IOP in patients who are using timolol, which has been previously shown for PGF_{2 α} -IE.^{10,11} The magnitude of the effect in the present study is better than in a previous study where 0.006% latanoprost was given twice daily for 1 month in otherwise untreated eyes.⁵ The results support the assumption that because of their different mechanisms of action the effects of timolol and latanoprost are completely additive.⁶

The present study also demonstrates that 0.006% latanoprost given once daily seems to be superior to twice daily administrations. Nagasubramanian *et al* made the same observation after 2 weeks of treatment with the same two dose regimens.⁴ As the results of two independent studies are the same it is unlikely that this is due to chance variation. Alternative explanations for this unusual response should be considered such as a dual effect of latanoprost on aqueous humour dynamics or the development of a moderate degree of receptor tolerance.

Latanoprost was administered in the evening to the once daily group and IOP was determined 12–20 hours later, whereas IOP determinations were made 4–8 hours after the dose in the twice daily group. Thus one obvious possibility is that latanoprost affects aqueous humour dynamics in more than one way, a short duration effect – less than 12 hours – which would increase IOP and a long duration IOP reducing effect. In early studies with PGF_{2 α} -IE an initial increase in IOP was observed, presumably due to intraocular vasodilatation.¹³ An intraocular vasodilatation and an increased episcleral venous pressure lasting for 8 hours is, however, an unlikely explanation to the difference between the two dose regimens. Latanoprost, unlike PGF_{2 α} -IE, has only a slight effect on intraocular blood flow.¹⁴ No dual effect on aqueous outflow has been observed for either PGF_{2 α} or latanoprost in monkeys; both increase uveoscleral flow without measurable effect on conventional outflow.^{14–17} A short duration increase of aqueous flow could explain the observed results, but previous studies both using PGF_{2 α} -IE and latanoprost have failed to demonstrate any effect on aqueous flow in the human eye.^{6,8,13,18} In those studies latanoprost was given alone and in the present study latanoprost was added to eyes with timolol suppressed aqueous flow, and the effect of latanoprost on aqueous flow in timolol treated eyes has not been determined. However, an increase of suppressed aqueous flow by latanoprost cannot explain the observation that the same difference between the two dose regimens was found in eyes not treated with timolol,⁴ and Ziai *et al* found that latanoprost had no effect on non-stimulated aqueous flow at night.⁸ Still,

none of these studies were designed to detect a small change in aqueous flow and the possibility that latanoprost causes an increase of aqueous flow of, for example, 10% for 8 to 12 hours cannot be excluded.

The other possibility, is a development of a moderate degree of receptor tolerance. One argument in favour of this explanation is that the difference between the two dose regimens is not seen until after a few days of treatment. In fact, Nagasubramanian *et al* found that 0.006% latanoprost given twice daily was significantly superior to the same dose given once daily on the second day of the study but significantly inferior after 14 days of treatment.⁴ Thus, the observed phenomenon that latanoprost given once daily seems to be superior to the same dose given twice daily may be based on development of some degree of receptor tolerance. Continued treatment after the first 2 weeks does not result in further loss of effect.

In the present study a small but statistically significant reduction in IOP also occurred in the contralateral eye. A drug related effect in the fellow eye cannot be expected with latanoprost as the dose given is very small and latanoprost is rapidly metabolised with a half life in plasma of only about 10 minutes.¹⁹ Some of the fellow eyes were being treated with timolol, but these eyes did not differ from untreated fellow eyes with respect to change in IOP during the study. Improved compliance during the study cannot explain the contralateral effect which was small and of no clinical significance. It perhaps is explained by a regression towards the mean since a lower limit for IOP was part of the inclusion criteria and the IOP of the two eyes tend to vary in concert.²⁰

Side effects were minimal in the present study. One patient interrupted the study owing to a keratitis that was judged as non-drug related. Flare was not observed in either group, and previous studies with various techniques have found no significant effect of latanoprost on the blood-aqueous barrier.⁸ A slight increase in conjunctival injection was noted, but was not clinically significant. There was no increase in ocular symptoms and no change in visual acuity or refraction. Thus there is a large difference in side effects between the phenyl substituted analogue latanoprost and its mother compound PGF_{2 α} -IE, which caused marked conjunctival hyperaemia and ocular irritation in large doses.¹³ In conclusion 0.006% latanoprost given once daily causes marked reduction of the IOP in patients being treated with timolol concomitantly, and administration once daily is not only adequate but probably superior to twice daily. Thus these results support the view that latanoprost may become a valuable addition to the treatment of glaucoma.

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