

# Additive effect of latanoprost, a prostaglandin F<sub>2α</sub> analogue, and timolol in patients with elevated intraocular pressure

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## Abstract

A randomised observer masked clinical study was conducted to assess the additive effect of latanoprost (13,14-dihydro-17-phenyl-18,19,20-trinorprostaglandin F<sub>2α</sub>-isopropylester) to timolol maleate in patients with elevated intraocular pressure (IOP). Patients were randomly assigned to two treatment groups. One group (n=10) received timolol, the other group (n=9) received latanoprost twice daily for 1 week. After 1 week all patients received both timolol and latanoprost. Eyes treated with timolol (mean diurnal IOP (SD) day 0, 24.2 (2.8) mm Hg) and latanoprost (mean diurnal IOP day 0, 28.5 (5.6) mm Hg) showed an IOP reduction of 5.9 (2.3) mm Hg (24%) and 8.9 (2.5) mm Hg (31%), respectively after the first week. Adding latanoprost to the eyes treated with timolol as well as timolol to the eyes receiving latanoprost gave a further reduction of 2.6 (1.1) mm Hg (13%) and 2.6 (2.2) mm Hg (14%), respectively. Only mild transient hyperaemia was observed in patients receiving latanoprost. The results indicate that latanoprost and timolol can be combined successfully and that complete or almost complete additivity is reached even at pressure levels below 20 mm Hg.

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Investigations using animal models have shown that prostaglandins (PG) can effectively lower intraocular pressure (IOP) in several species including primates.<sup>1-5</sup>

Although subsequent studies in normotensive and glaucomatous eyes showed that topical application of PGF<sub>2α</sub> and prostaglandin F<sub>2α</sub>-isopropylester (PGF<sub>2α</sub>-IE)<sup>7-9</sup> can effectively lower IOP in human subjects, dose dependent conjunctival hyperaemia and local irritation prevented their use.<sup>6</sup> Recently it has been reported that certain phenyl substituted prostaglandin analogues induce an effective IOP reduction with fewer side effects.<sup>10</sup> In particular, PhXA34 (13,14-dihydro-15(R,S)-17-phenyl-18,19,20-trinor-PGF<sub>2α</sub>-isopropylester)<sup>11,12</sup> and latanoprost<sup>13-15</sup> (its 15-R epimer) have been reported to decrease IOP at low concentrations with fewer side effects. Two recent studies<sup>16,17</sup> showed a marked additive effect of PGF<sub>2α</sub>-IE when combined with timolol. We were, therefore, interested in the combination therapy with latanoprost and timolol.

The purpose of this study was to evaluate the efficacy and side effect profile of latanoprost as single therapy and in combination with the β adrenergic antagonist timolol.

## Patients and methods

Twenty patients were selected at the outpatient clinic of the glaucoma centre of the University of Amsterdam. The inclusion criteria were age over 18 years, bilateral ocular hypertension, or early primary open angle glaucoma (Aulhorn's classification II) with two or more independent IOP measurements of 22 mm Hg or higher. Female patients were admitted to the study if they were post-menopausal or used adequate contraceptives.

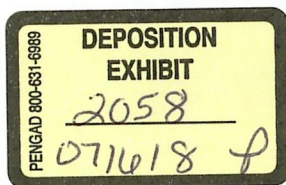
Exclusion criteria were: history of angle closure, severe ocular trauma, intraocular surgery or argon laser trabeculoplasty, use of contact lenses, history of infection and/or inflammation during 3 months preceding the study, or severe dry eye syndrome. Other exclusion criteria were use of systemic or ocular medication known to affect IOP, cardiac, or pulmonary diseases, as well as diabetes mellitus requiring insulin therapy.

The trial was designed as a randomised, observer masked study evaluating the additive effect of latanoprost and timolol in two parallel groups with two consecutive treatment periods of 1 week each. Before the study patients underwent a washout period of 8 days or longer for sympathicomimetics, 14 days or longer for cholinergic agents, and 21 days or longer for adrenergic antagonists. In the first week of the study, patients in group A administered one drop (approx 35 μl) of latanoprost in both eyes between 700 am and 900 am and one drop between 700 pm and 900 pm. In the second week timolol was administered after latanoprost with a 5 minute interval.

Patients in group B started with timolol, one drop in both eyes between 700 am and 900 am and one drop between 700 pm and 900 pm. After the first week latanoprost was added 5 minutes after timolol was administered.

Commercially available timolol (Timoptol 0.5%, MSD, Haarlem, the Netherlands) was used and latanoprost (0.006%: 60 μg/ml) was provided by Kabi Pharmacia, Uppsala, Sweden.

All IOP measurements were performed using a Goldmann applanation tonometer, with the scale masked for the investigator. The tonometer scale was read by an assistant. Three consecutive IOP measurements per eye were taken. Hyperaemia was graded 0 indicating absence of hyperaemia, 1 mild, 2 moderate, and 3 severe hyperaemia. Half steps were used when appropriate. Standard photographs were used to grade conjunctival hyperaemia. Medical and ocular history were obtained from all patients before entering the study. Subsequently all patients underwent slit-lamp biomicroscopy, fundu-



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scopy, Humphrey (Allergan, San Leandro, CA, USA) 24/2 visual field examination, hyperaemia grading, and IOP measurements. Blood pressure and pulse rate were also recorded.

On days 0, 2, 7, 9, and 14 the patients arrived in the glaucoma centre between 8 00 am and 9 00 am. After recording any general or ocular symptoms, hyperaemia was graded using the standard photographs for comparison. Thereafter three consecutive IOP measurements of each eye were taken. This procedure was repeated at noon and 4 00 pm. Visual acuity, blood pressure, and pulse rate were recorded during the 8 00 am visits. Both blood pressure and pulse rate were measured three times consecutively. After day 14 a post-study examination was performed. This examination was identical to the pre-study examination. Diurnal IOP values were obtained by calculating the mean of the 8 am, noon, and 4 pm IOP values for each patient.

The IOP values, pulse rate, and blood pressure were expressed as the arithmetical mean (SD). The primary objective of the study was to test whether latanoprost and timolol exert additive effects on IOP. The null hypothesis accordingly was defined as the diurnal IOP reduction on day 7 (monotherapy) being equal to the diurnal IOP reduction on day 14 (combined therapy) from the diurnal IOP on day 0. The alternative hypothesis was that the combination further reduced the IOP with at least 2 mm Hg compared with treatment with only one drug. The further reduction was presumed to represent the additive effect of the second drug since the effect on the first drug was assumed to be stable after 7 days of treatment. The IOP reduction was tested with analysis of covariance with baseline IOP as covariate. A comparison of the mean IOP reductions between the treatment groups was performed on days 7 and 14 using three way analysis of covariance with patients, days, and treatment groups as factors and baseline IOP as covariate. Wilcoxon's rank sum test was used for analysis of hyperaemia. Differences with a *p* value <0.05 were considered significant. The changes in blood pressure and pulse rate were analysed statistically with the matched paired *t* test, comparing the values during treatment with those on baseline.

The study was approved by the ethics review board of the Academic Medical Center, Amsterdam and each patient gave written informed consent before entering the study. The study was performed in accordance with the principles adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and later revisions.

### Results

Ten patients were allocated to latanoprost treatment (group A) and 10 patients to timolol treatment (group B). One patient in group A was excluded because it was found out that the patient had undergone only 2 days instead of 2 weeks washout of pilocarpine and acetazolamide. There were no major differences between the groups with regard to the demographic characteristics such as mean age and male/female ratio, but IOP at day 0 differed markedly between the groups (Table 1).

In the group using latanoprost maximum IOP lowering effect was seen on day 2 (Fig 1). On day 7 an IOP reduction of 8.9 (2.5) mm Hg (*p*<0.01) was observed in the latanoprost group compared with a reduction of 5.9 (2.3) mm Hg (*p*<0.01) in the timolol group (31% and 24% respectively). This difference in IOP reduction between the groups was not significant. The combined therapy revealed an additional IOP reduction compared with either drug administered alone. Latanoprost added to timolol further reduced IOP on day 14 compared with day 7 2.6 (2.2) mm Hg (*p*<0.01) and timolol added to latanoprost further reduced IOP 2.6 (1.1) mm Hg (*p*<0.01).

Conjunctival hyperaemia compared with baseline was especially seen in the latanoprost treatment group on day 2 (Table 2). On day 7, less conjunctival hyperaemia was registered than on day 2. When latanoprost was added to timolol conjunctival hyperaemia increased slightly compared with day 7, being more pronounced on day 9. No changes in hyperaemia were observed when timolol was added to latanoprost. The difference in hyperaemia between the two groups was, however, not statistically significant on days 2 and 7 (*p*>0.05, Wilcoxon rank sum test).

Latanoprost was well tolerated in the study. Stinging sensations after both latanoprost and timolol were noted in a few patients. The heart rate was reduced with 5.8 (6.9) min<sup>-1</sup> (*p*<0.05) on day 7 and 6.9 (8.8) min<sup>-1</sup> (*p*<0.05) on day 14 compared with day 0 in the timolol-latanoprost group. There was no significant effect on the systolic or diastolic blood pressure in either group.

### Discussion

Previous studies using other prostaglandin analogues such as PGF<sub>2α</sub>-IE were hampered by clinically unacceptable grades of conjunctival hyperaemia, local irritation, and pain sensation when optimal IOP lowering doses were administered.<sup>6</sup> Latanoprost, a new PGF<sub>2α</sub> analogue, seems to have markedly fewer side effects as reported in previous studies.<sup>9,13-15</sup>

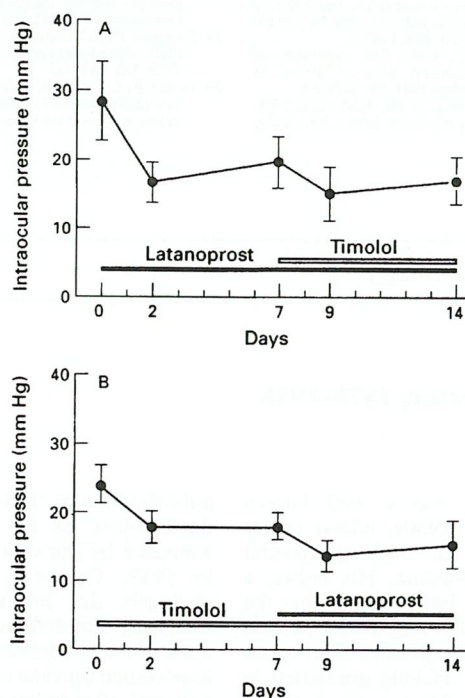
The main mechanism of action to account for the reduction in IOP following administration of prostaglandin F<sub>2α</sub> and its analogues is thought to be an increase in uveoscleral outflow<sup>18-20</sup> and not

Table 1 Demographic and clinical characteristics of the treatment groups

	Latanoprost	Timolol
Age		
Mean (range)	61.2 (47-84)	64.1 (40-82)
Sex		
Male/female	5/5	3/7
Race		
White	9	10
Asian	1	0
Iris colour		
Blue/green	8	9
Brown	2	0
Grey	0	1
Diagnosis		
Ocular hypertension	9	9
Glaucoma	1	1
Duration (months)		
Median (range)	55 (2-350)	48 (2-140)
Previously treated	8	4
Intraocular pressure		
Mean (SD) (mm Hg)	28.5 (5.6)	24.2 (2.8)



Figure 1 (A) Intraocular pressure reduction (mean (SD)) in group A, starting with latanoprost 60 µg/ml twice daily. Adding timolol 0.5% twice daily to latanoprost in the second week gave a further IOP reduction of 2.5 mm Hg (13%). (B) Intraocular pressure reduction (mean (SD)) in group B, starting with timolol 0.5% twice daily. Adding latanoprost 60 µg/ml twice daily to timolol in the second week gave a further IOP reduction of 2.5 mm Hg (14%).



an increase in true trabecular outflow or an inhibition of aqueous humour formation. Therefore, when PGF<sub>2α</sub> analogues are being combined with agents like timolol which reduce IOP by an inhibition of aqueous humour production, an additive effect may be expected.

In a previous study by Villumsen and Alm<sup>16</sup> an additive effect of approximately 30% was found when PGF<sub>2α</sub>-IE was administered to patients on timolol treatment having a mean IOP of 25 mm Hg. In another study by Lee *et al*<sup>17</sup> ocular hypertensive patients with very high initial IOPs (>40 mm Hg) had a mean IOP of 27 mm Hg after 1 week of timolol treatment. In their study PGF<sub>2α</sub>-IE also induced a similar additive effect when combined with timolol indicating more or less complete additivity of PGF<sub>2α</sub>-IE to timolol.

Although the combination of timolol and latanoprost induced an IOP lowering effect of not more than 13–14%, in contrast with previous observations, complete additivity may be present assuming that latanoprost is less effective at lower IOP levels.

In both groups there was an upward drift in IOP during latanoprost treatment. Such an upward drift in IOP has previously been reported during latanoprost treatment.<sup>14</sup> However, we do not believe that this phenomenon has affected the results significantly as the drift is

seen mainly during the first week of treatment.<sup>14</sup>

As a single therapy latanoprost effectively reduced IOP in this study. Maximum IOP lowering effect was observed after 2 days of treatment, the decline in IOP being 42%; after 1 week an IOP reduction of 31% was present in patients with a mean initial IOP of 28.5 mm Hg. In the timolol group an IOP reduction of 24% was observed during the first week of treatment. The difference in baseline IOP between the treatment groups makes a comparison in efficacy of both drugs difficult. However, the results indicate that latanoprost 60 µg/ml twice daily is at least as effective in reducing IOP as timolol 5 mg/ml twice daily.

In patients on PGF<sub>2α</sub>-IE an inconvenient hyperaemia and local discomfort have been reported.<sup>6,17</sup> In this study, a slight hyperaemia was noted in half the patients on latanoprost. No significant ocular discomfort or evidence of pain sensation were observed. Latanoprost was well tolerated by all patients and the slight hyperaemia did not cause them to withdraw from the study. Hence, latanoprost, unlike PGF<sub>2α</sub>-IE, is not hampered by clinically unacceptable ocular side effects. In contrast with timolol, latanoprost had no significant effect on the heart rate which is a clear advantage.

If long term studies can demonstrate a sustained IOP reducing effect with latanoprost, it will be a valuable new drug in the therapeutic arsenal of glaucoma management.

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Table 2 Hyperaemia score in the two treatment groups

Hyperaemia score	Group A					Group B						
	0	1.0	2.0	3.0	0	1.0	2.0	3.0	0	1.0	2.0	3.0
Day 0	2	7				6	4					
Day 2	1	4	2	1		6	4					
Day 7	4	2	3			8	2					
Day 9	1	6	2			3	2	3	2			
Day 14	2	6	1			4	5			1		

The data indicate the numbers of patients with a given hyperaemia score.



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## History of ophthalmology

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### John Martin Wheeler, 1879-1938

John Martin Wheeler was a well known ophthalmologist in the 1930s, whose career encompassed episodes of both spectacular good fortune and misfortune. His father, a country lawyer who had fought in the American civil war, could only afford to send his son to the small, inexpensive Burlington University of Vermont. Having graduated in arts and medicine, Wheeler was very lucky to obtain his ophthalmological internship in New York in 1909. During training, he was remarkable for his diligence and his manual dexterity. Constantly having good ideas for papers and reports, he was so hesitant and cautious that most of these ideas were eventually taken up and published by colleagues – which he never minded!

His forte was meticulous surgical technique, in which he was inspired by his boss, D W Hunter. One of Hunter's most daring procedures was the opening of secondary cataract by running a Graefe knife along the membrane in a single, rapid act of forearm supination. Wheeler describes the result as 'sure and beautiful'. He combined his admiration with pragmatism, in noting that most of the surgeons who came to watch Hunter were too terrified of slashing the cornea to use the technique themselves. Wheeler then developed a less risky method, which he published in the *British Journal of Ophthalmology*, with meticulous pencil drawings of exactly how the operator's thumb and forefinger should rest on the knife. The reader was exhorted to keep the hand and wrist joints perfectly immobile, creating the incision by a 'a rapid, free' movement of the whole arm. If correctly done, 'the knife handle should rotate as if impaled on a pin', and full drawings of the hypothetical pin's position were included.

Wheeler frequently stated that the surgeon should have nothing less than a keen and faultless knife with which to ply his trade, and that this should be ground to perfect sharpness. One can imagine his wrath when anything less was found on his instrument table.

During the first world war, Wheeler entered the medical corps and the care of blinded and disfigured veterans turned his interest permanently towards plastic surgery, on which he

published many of the landmark papers of the time. Most of his patients were soldiers wounded by gunshot or explosives in France in 1918. Operating under ether, Wheeler obviously did his utmost to repair facial fractures, skin defects, and the hasty exenterations of the battlefield, constantly aware of the importance (in view of the extreme youth of his patients) of good cosmetic results.

Returning to civil practice, Wheeler's stroke of good fortune occurred. The King of Siam, arriving in New York with his retinue, chose Wheeler to operate on his eye. Although many of his colleagues must have felt extreme envy, the quiet and retiring Wheeler found the media interest quite distressing, miserably trying to evade the press when arriving at the hospital. The King was delighted with the result and in 1931 awarded a protesting Wheeler the Commander of the Order of the Cross of Siam. He could literally have made a fortune in private practice from then on . . . However, having his log cabin in Vermont as a holiday home, and sufficient equipment for golf, he felt no need for a fortune, and coolly cut back his private practice to concentrate on postgraduate teaching. This must have amazed his envious colleagues, and probably arouses incredulous feelings still.

Tragedy then struck, in the form of a choroid sarcoma which necessitated the removal of John Wheeler's left eye. It seemed that a great operative talent would be lost, yet he adapted to this and continued to show the same degree of manual dexterity. (His patients' reactions on learning that their surgeon had only one eye are not recorded.) Because of his fame and the value of his pioneering work, Wheeler's death three years later was noted widely by ophthalmologists and plastic surgeons. Both specialties continued to profit from his operative techniques for long afterwards.

FIONA ROMAN

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