Latanoprost versus combined therapy with timolol plus dorzolamide: IOP-lowering effect in open-angle glaucoma

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ABSTRACT.
Purpose: **To compare the effect on intraocular pressure of latanoprost versus timolol plus dorzolamide in open-angle glaucoma.**
Methods: **Thirty-five patients with open-angle glaucoma were randomized, 18 to latanoprost once daily and 17 to timolol plus dorzolamide twice daily. Intraocular pressure and ocular side effects were recorded at baseline, and after 2 weeks and 3 months of treatment.**
Results: **Latanoprost reduced the intraocular pressure 1.09 and 1.58 mm Hg more than timolol plus dorzolamide after 2 weeks and 3 months of treatment, respectively. These differences were statistically significant ($p < 0.05$) at the end of the study. After 3 months of treatment, 32.3% of the eyes in the latanoprost group reduced the intraocular pressure in 30% or more with respect to baseline, while 15.6% of the eyes in the timolol plus dorzolamide group achieved this reduction.**
Conclusions: **Latanoprost administered once daily reduced the intraocular pressure at least as well as timolol plus dorzolamide twice daily in patients with open-angle glaucoma.**

Key words: latanoprost – timolol – dorzolamide – intraocular pressure – treatment.

Glaucoma is a progressive optic neuropathy with characteristic optic nerve head changes and decrease in retinal sensitivity that lead to visual loss (Fetchner & Weinreb 1994).

Once the disease is diagnosed, treatment is required to stop progressive damage (McClellan 1995; Capino & Leibowitz 1990; Coyle & Drummond 1995), and, generally, medical treatment is the first therapeutic approach (Sherwood et al. 1993). Beta-adrenergic antagonists, like timolol (Epstein et al. 1989; Frishman et al. 1994), have been considered for many years as the drugs of choice in most cases, while other agents, like adrenergic agonists (Bill 1970; Allen 1986) and parasympatico-mimethic agents (Bill 1967; Quigley et al. 1975) were used as second-line drugs. However, new drugs have been introduced for glaucoma treatment, like selective alpha agonists (Gross et al. 1997; Toris et al. 1995), carbonic anhidrase inhibitors (Centofanti et al. 1997; Pfeiffer 1997) and prostaglandins (Hotehama et al. 1993; Fristrom & Nilsson 1993), broadening the therapeutic choices.

Latanoprost (13,14-dihydro- 17-phenyl-18,19,20-trinor-prostaglandin F2a – isopropil-ester) is a prostaglandin analogue that produces an ocular hypotensive effect (Hotehama et al. 1993; Friström & Nilsson 1993; Alm et al. 1994; Ziai et al. 1993). It has been established that the major mechanism of action is an increased uveoscleral outflow (Giuffré 1985; Gabelt & Kaufman 1989; Nilsson et al. 1989) with little or no effect on aqueous humor flow (Toris et al. 1993).

The purpose of this study was to compare the intraocular pressure (IOP) reducing effect of latanoprost (once daily) versus the combined therapy with timolol plus dorzolamide twice daily in patients with open-angle glaucoma.

Methods

Patients

A total of 35 patients from the Glaucoma Unit of our Department of Ophthalmology ("Miguel Servet" Hospital, Zaragoza, Spain) were enrolled in the study. Patients over 18 years old on monotherapy with beta-blockers and open-angle glaucoma or exfoliative glaucoma were eligible for the study. The intraocular pressure (IOP) was higher than or equal to 22 mmHg in patients with glaucoma and above 27 mmHg in ocular hypertensives.

Patients were excluded if they received dorzolamide or latanoprost previously, any dual or multiple treatment for glaucoma, had undergone eye surgery or laser treatment 3 months prior to the study, suffered from closed-angle glaucoma, experienced ocular infection or inflammatory ocular disease 3 months prior to the study or referred hypersensitivity to benzalkonium chloride. Other exclusion criteria were cardiovascular or bronchial disease, pregnancy, or inability to attend the follow-up visits.

The study was approved by the "Miguel Servet" Hospital Ethics Committee. The patients were informed about the risk of the study and signed informed consents were obtained.

Table 1. Schedule of examinations.

Elegibility Timolol al 0.5%, twice daily	Latanoprost 0.005%, once daily (night)
	Timolol 0.5%, twice daily Dorzolamide 2%, twice daily

Elegibility	Baseline	Week 2	Month 3

Table 2. Characteristics of the study groups.

Characteristics	Latanoprost (n=18)	Timolol+Dorzolamide (n=17)
Age		
Mean±DS	60.1+16.4	66.3+8.7
Range	24–95	51–81
Sex		
M	13 (72%)	5 (29%)
F	5 (28%)	12 (71%)
Familiar history	6 (33%)	7 (41%)
Number of eyes per patient		
1 eye	2 (11%)	2 (12%)
2 eyes	16 (89%)	15 (88%)
Iris color		
Brown	22 (65%)	28 (87%)
Blue/Green/Gray	8 (24%)	2 (11%)
Mixed	4 (11%)	2 (11%)
Diagnosis		
POAG	17 (94%)	16 (94%)
Exfoliative glaucoma	1 (6%)	1 (6%)

Table 3. Differences in intraocular pressure values (mean±standard deviation) during the study. "Δ IOP": Difference in mmHg to baseline IOP.

Group of treatment	Baseline	Week 2	Months 3
IOP			
Latanoprost	22.06±3.06	16.56±2.76	16.77±2.2
Timolol+Dorzolamide	22.44±4.85	17.81±3.01	18.1±3.51
ΔIOP			
Latanoprost	–	5.22±2.47	4.97±2.42
Timolol+Dorzolamide	–	4.13±3.41	3.39±2.48

Study schedule and procedures

The study was designed and computer-randomized by Pharmacia & Upjohn and is part of a multicentric, open, and parallel study conducted in Spain.

During the month preceding the start of the study (baseline day), patients were assessed for eligibility. The examination procedure included visual acuity, refraction, slit lamp examination, intraocular pressure determination and fundus evaluation. All patients changed to or initiated treatment with timolol 0.5% twice daily (provided by Pharmacia & Upjohn). The treatment was administered for at least two weeks before the baseline day.

On baseline visit, the eligible patients were randomly assigned to treatment. One group of patients received latanoprost 0.005% once daily and the other group received timolol 0.5% and dorzolamide 2% twice daily.

The examination schedule is presented in Table 1, and included 3 visits: on baseline day, and after 2 weeks and 3 months, respectively.

Results

A total of 35 patients were included in the study. Eighteen subjects were randomly assigned to treatment with latanoprost, while 17 subjects received timolol plus dorzolamide.

Table 2 presents patient demographics. The descriptive data showed no statistical differences between both groups of treatment.

Effect on intraocular pressure

The treatment in both groups reduced significantly ($p < 0.001$) the average diurnal IOP at baseline visit and after 2 weeks and 3 months, with respect to baseline IOP (Fig. 1 and Table 3).

Latanoprost reduced 1.09 and 1.58 mmHg more than timolol plus dorzolamide after 2 weeks and 3 months of treatment, respectively. At the end of the study, the differences were near to statistical signification ($p < 0.1$) as shown in Table 3.

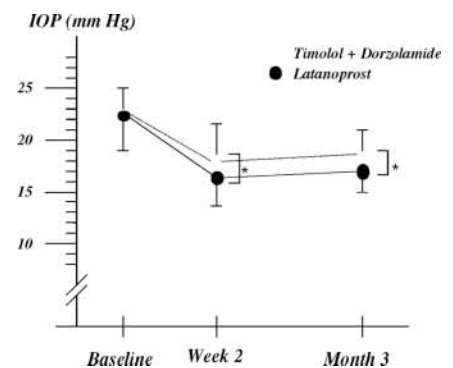Fig. 2 shows the IOP reduction in percentages with respect to baseline IOP.

Fig. 1. IOP reduction achieved with latanoprost 0.005% administered once daily and timolol 0.5% plus dorzolamide 2%, twice daily (mean±standard deviation) (*$p < 0.1$).
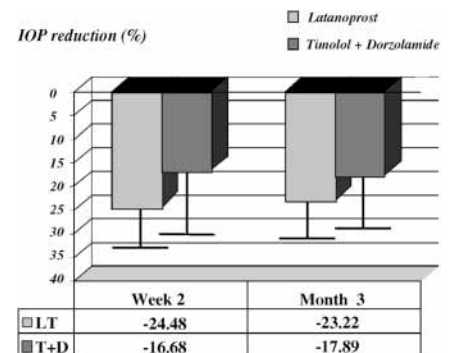

	Week 2	Month 3
LT	-24.48	-23.22
T+D	-16.68	-17.89

Fig. 2. Percentages of reduction of IOP with respect to baseline.

Table 4. Intervals of IOP reduction (in percentages) with respect to baseline IOP.

	Week 2		Month 3	
	LT	T+D	LT	T+D
0%–10%	3 (8.8%)	7 (21.8%)	5 (14.7%)	7 (21.8%)
10%–20%	11 (32.3%)	10 (31.2%)	6 (17.6%)	10 (31.2%)
20%–30%	10 (29.4%)	8 (25%)	12 (35.2%)	10 (31.2%)
30%–40%	10 (29.4%)	7 (21.8%)	11 (32.3%)	5 (15.6%)
	34 (100%)	32 (100%)	34 (100%)	32 (100%)

Table 5. Ocular side effects.

Ocular side effects	Latanoprost (n=18)	Timolol+Dorzolamide (n=17)
Foreign body sensation	1 (5%)	0 (0%)
Itching	3 (16%)	1 (5%)
Burning	2 (11%)	1 (5%)
Tearing	0 (0%)	0 (0%)
Conjunctival hyperemia	2 (11%)	1 (5%)
Pain	1 (5%)	0 (0%)
Photophobia	0 (0%)	0 (0%)

After 2 weeks of treatment, latanoprost reduced the baseline IOP in 24%, while timolol plus dorzolamide reduced 17% (p<0.1). At the end of the study (3 months) the percentages of reduction were 23% and 18%, respectively (p<0.01).

The analysis of intervals of reduction, in percentages, showed that 10 out of the 34 eyes (29.4%) included in the latanoprost group reduced their IOP more than 30% with respect to baseline after 2 weeks of treatment, while timolol plus dorzolamide achieved this reduction in 7 of 32 eyes (21.8%) (Table 2). After three months of treatment the difference increased to 32.3% (11 of 34) for the latanoprost group and 15.6% (5 of 32) for the timolol plus dorzolamide group (Table 4).

Ocular side effects

Table 5 shows the symptoms and signs observed during the study. There were no relevant adverse effects.

The most frequent complaints were itching and burning. Their incidence was slightly superior in the latanoprost group. A mild conjunctival hyperemia was also more frequent in this group.

Latanoprost did not produce significant aqueous flare, anterior chamber cellular response, visual acuity alterations or changes in iris color.

Discussion

Latanoprost is a prostaglandin lipophilic ester analogue that remains inactive until enzymatic hydrolysis at corneal tissue, which activates the drug. Latanoprost incorporates substantial changes in its molecular structure that improve the selectivity and action of the drug at the prostanoid FP receptors and increases the therapeutic index of the drug for glaucoma treatment (Stjernschantz & Resul 1992; Resul et al. 1993; Alm et al. 1993; Nagasubramanian et al. 1993).

Since this drug was introduced, there had been several reports about the hypotensive effect of the drug compared to other antiglaucomatous agents. Four multicentric longitudinal studies had been carried out (Mishima et al. 1996; Watson & Stjernschantz 1996; Camras 1993; Alm & Stjernschantz 1995) to compare the effect of latanoprost once daily to timolol twice daily in ocular hypertensives and glaucoma patients with IOP greater than 20 mmHg. It has been established that latanoprost obtains greater IOP reduction than timolol (Mishima et al. 1996; Watson & Stjernschantz 1996; Camras 1993; Alm & Stjernschantz 1995). This reduction ranges from 27% to 35% with latanoprost and 19% to 33% with timolol with respect to baseline IOP.

In our study, the hypotensive effect of latanoprost has been compared to that of the dual therapy with timolol plus dorzolamide twice daily. Latanoprost showed to be more effective than the dual therapy. The prostaglandin analogue achieved a lower average IOP at the end of the study (4.97 versus 3.39 mmHg, p<0.05) and the IOP reduction with respect to baseline was 23.22% for latanoprost and 17.89% for timolol plus dorzolamide.

These results are in general agreement with another study (Emmerich KH, 1998, non published data) that suggested that latanoprost could be an alternative to dual therapy of timolol plus dorzolamide.

The percentage of subjects with IOP reduction higher than 30% with respect to baseline was higher in patients treated with latanoprost. Also, the analysis of IOP reduction in intervals showed that, between the 2nd week and the 3rd month, latanoprost increased the number of eyes with reductions higher than 30%, while the dual therapy decreased its figures. This is in agreement with other authors who showed that latanoprost reduces the IOP progressively during the first months of treatment (Watson & Stjernschantz 1996). This may be due to the intrinsic mechanism of action of the substance. At the cilliary body, prostaglandins induce the secretion of enzymes called metaloproteases that reduce the resistance to uveoscleral outflow (Lindsey et al. 1997). Possibly, the synthesis of enzymes increases during the first weeks of treatment, inducing a progressive IOP reduction.

On the contrary, in the timolol plus dorzolamide group some patients shifted from the 30% of IOP reduction to lower percentages of reduction along the follow-up. It is known that timolol obtains long-lasting hypotensive effects. Therefore, dorzolamide could be responsible for the progressive loss of efficacy of the dual therapy. This drug would add a hypotensive effect to timolol during the first weeks, while losing effect in the following months.

It is the belief of the authors that the analysis of the data by intervals of reduction, instead of mean and standard deviation, improves the analysis and interpretation of the data because it compares the results of the treatment to the individual baseline IOP. These intervals of reduction showed that latanoprost achieved higher IOP reductions without losing effect. This fact is particularly relevant if we consider that the study compares a monotherapy once daily against a dual

therapy twice daily, and therefore, latanoprost obtains maximum efficacy with minimum therapy.

In past years, the incidence of ocular adverse effects had been a drawback for the use of these drugs, like the prostaglandin analogues of PGF2 which presented a low tolerability (Sherwood et al. 1993; Villumsen et al. 1989; Lee et al. 1988). Later, modifications of the molecular structure increased the therapeutic effect of the drug and decreased its side effects (Stjernschantz & Resul 1992; Resul et al. 1993; Alm et al. 1993; Nagasubramanian et al. 1993). Latanoprost is a highly selective agonist of FP receptors, with very low interaction with other receptors which avoids the lateral effects.

In our study, the most frequent ocular side effects were itching, burning and foreign body sensation, especially in the latanoprost-treated group. The incidence of these symptoms was similar to other studies (Mishima et al. 1996). The presence of conjunctival hyperaemia was lower compared to other reports (Mishima et al. 1996), but in these reports, latanoprost or its vehicle was instilled twice daily to double-mask the study. The vehicle contains benzalkonium chloride which is irritant to the conjunctiva and could account for the increased hyperaemia.

In conclusion, the results of our study show that latanoprost administered once daily reduced the intraocular pressure at least as well as timolol plus dorzolamide twice daily in patients with open-angle glaucoma.

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