Efficacy and safety of timolol maleate/latanoprost fixed combination versus timolol maleate and brimonidine given twice daily

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ABSTRACT.

Purpose: **To evaluate the efficacy and safety of the timolol maleate/latanoprost fixed combination (TLFC) given once each evening versus brimonidine and timolol solution given twice daily as concomitant therapy in primary open-angle glaucoma or ocular hypertension patients.**

Methods: **Qualified subjects were begun on timolol alone twice daily for 1 month and then randomized to either TLFC or brimonidine and timolol concomitant therapy for 6 weeks. Patients were then switched to the other treatment regimen. Intraocular pressures (IOPs) were measured every 2 hours between 08 : 00 and 20 : 00 hours at baseline and at the end of periods 1 and 2.**

Results: **This study found that in 32 subjects the IOP diurnal curve on timolol alone (20.9 ± 2.8 mmHg) decreased to 17.9 ± 3.2 mmHg when patients were treated with TLFC and to 19.0 ± 2.4 mmHg when patients were treated with brimonidine and timolol ($p = 0.02$). Intraocular pressures at individual time-points were statistically similar between the groups at the 08 : 00 trough and 2 and 4 hours after dosing. However, beyond 4 hours after dosing, TLFC-treated subjects demonstrated a trend towards lower IOPs at each 2-hour time-point that was not statistically significant after a Bonferroni correction ($p \leq 0.05$). The incidence of both solicited and unsolicited side-effects was similar between groups.**

Conclusion: **This study suggests that TLFC given in the evening reduces the mean daytime diurnal IOP more than brimonidine and timolol given concomitantly twice daily.**

Key words: timolol/latanoprost – brimonidine

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Introduction

Latanoprost, released commercially several years ago, is an analogue of an $F_2\alpha$ prostaglandin and is highly selective for the FP receptor (Stjernschantz & Resul 1992). Latanoprost has been shown to be more effective in reducing daytime intraocular pressures (IOPs) than timolol maleate given twice daily in Scandinavian, US and Japanese regulatory trials (Alm & Stjernschantz 1995; Camras 1996; Mishima et al. 1996), but not in UK regulatory trials (Watson & Stjernschantz 1996). It has also been shown to be more effective than unoprostone in reducing IOP (Susanna et al. 2001).

Further, Stewart et al. (2000) reported in a retrospective trial that latanoprost statistically reduced IOP more than brimonidine (approximately 4 mmHg versus 2 mmHg). More recently, a prospective study by Stewart et al. (2001) showed that, over the 12-hour daytime diurnal curve, latanoprost statistically reduced IOP more than brimonidine at each time-point. In this study, brimonidine, given twice daily, decreased IOP from baseline for 8 hours post-dosing (Stewart et al. 2001).

Stewart et al. (2001) demonstrated retrospectively that latanoprost as adjunctive therapy reduced IOP statistically more (6.2 mmHg) than brimonidine (4.2 mmHg) when both were added to timolol maleate. However, little information evaluating latanoprost versus brimonidine added to timolol maleate is available prospectively (Stewart et al. 2001).

The purpose of this current trial was to compare the efficacy and safety of latanoprost and timolol maleate in the new fixed combination treatment (Xalacom®, Pharmacia Inc., Peapack, New Jersey, USA) versus brimonidine 0.2% (Alphagan®, Allergan, Irvine, California, USA) and timolol maleate 0.5% solution, each given twice daily, in primary open-angle glaucoma or ocular hypertension patients.

Materials and Methods

Patients

Patients included in this study had to be aged 18 years or older, be willing to comply with the investigators' and the protocol's instructions and to sign the informed consent form. The subjects had to demonstrate a clinical diagnosis of primary open-angle, pigment dispersion or exfoliation glaucoma, or ocular hypertension in at least one eye (the study eye). The subjects were required to have a baseline IOP of between 21 and 34 mmHg in the study eye at 08 : 00 at visit 2 while dosing with timolol maleate twice daily (IOP in the non-study eye had to be controlled on either no pharmacological therapy or the study medication). The subject needed to have visual acuity (VA) of 20/200 or better in both eyes.

We excluded patients with any of the following: any abnormality preventing reliable applanation tonometry in the study eye(s); any opacity or patient non-cooperativeness that restricted adequate examination of the ocular fundus or anterior chamber in the study eye; any concurrent infectious/non-infectious conjunctivitis, keratitis or uveitis in either eye; any history of allergic hypersensitivity or poor tolerance to any components of the preparations used in this trial; any female who was pregnant or lactating and those of childbearing potential not using reliable means of birth control; any clinically significant, serious or severe medical or psychiatric condition; any intraocular conventional surgery or laser surgery within the previous 2 months in the study eye(s); unacceptable risk of visual field or VA worsening as a possible consequence of participation in the trial; current therapy with monoamine oxidase inhibitors (MAO) inhibitors or tricyclic antidepressants; progressive retinal or optic nerve disease apart from glaucoma; history of bronchial asthma; severe chronic obstructive pulmonary disease; sinus bradycardia; second or third degree atrioventricular block; overt cardiac failure; cardiogenic shock; any anticipated change in systemic hypotensive therapy during the active treatment portion of the trial; unwillingness to accept a risk of iris colour or eyelash changes, and inability to understand the trial procedures and give informed consent. Subjects could not have participated (or have current participation) in any other investigative drug or device trial within the 30 days prior to the baseline visit of the trial.

Procedures

All patients signed an informed consent document approved by the Institutional Review Board before any procedures were performed. At least 28 days prior to baseline, subjects underwent a screening examination (visit 1) that consisted of an ocular and systemic history, gonioscopy, a visual field (Humphry Field Analyser, Program 24–2, San Leandro, California, USA) and dilated ophthalmoscopy. As at other visits in this trial, they also underwent slit-lamp biomicroscopy, Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity and Goldmann applanation tonometry. If patients met the inclusion/exclusion criteria, their current glaucoma medication was discontinued and they were placed on timolol maleate 0.5% twice daily. Patients were then asked to return in 4 weeks for the baseline visit.

At visit 2 (day 0, baseline visit) patients had to demonstrate an IOP on timolol maleate of between 21 and 34 mmHg in at least one eye. They then underwent baseline diurnal curve IOP measurements every 2 hours from 08 : 00 to 20 : 00 hours and completed symptom surveys. They were then randomly assigned to the masked study medication, which consisted of either one bottle of the timolol maleate/latanoprost fixed combination (TLFC) and one bottle of placebo (Hypotears®, Novartis Ophthalmics, Atlanta, Georgia, USA) dosed every evening and two bottles of placebo dosed every morning, or brimonidine 0.2% and timolol maleate 0.5% both dosed twice daily at 08 : 00 and 20 : 00 hours. Patients were asked to administer the medications 5 min apart. Both study personnel and patients were masked to the medication.

Patients returned after 2 weeks for a safety check at visit 3, and then again after 4 weeks for the end of period 1 diurnal curve IOP measurements and symptom surveys (visit 4). Patients were dosed with the period 1 study medicine after the 08 : 00 trough pressure measurement before the diurnal curve was measured. Subjects were then switched to period 2 medication. They then returned after 2 weeks for the period 2 safety check (visit 5) and then again in 4 weeks for the end of period 2 assessments, which included diurnal curve IOPs and symptom surveys performed as in period 1 (visit 6). Subjects were then exited from the study.

Statistics

The diurnal IOP between the efficacy visits 4 and 6 were analysed by a paired *t*-test for intragroup analysis and a repeated measures of analysis. The pressures at individual time-points were also analysed by a paired *t*-test. An average eye analysis was used. A 0.05 alpha level was used to declare significance (Book 1978). A Bonferroni correction was used to adjust the p-value at individual time-points. The standard deviation used to determine the power was 2.8 mmHg (Duff 1987; Mundorf et al. 1998; Stewart et al. 1999, 2000). This study, with 30 patients, provided at least an 80% power so that a 1.5 mmHg difference could be excluded between groups. Thirty-two patients were entered to ensure that 30 were available for an intent-to-treat analysis. A two-sided comparison was used to compare treatments and a one-sided comparison was used from baseline.

Safety parameters for intragroup analysis were evaluated with a Wilcoxon sign rank test that included ocular as well as systemic symptom queries (Book 1978). Visual acuity was analysed by a paired *t*-test (Book 1978). Adverse events and the number of

patients who reached specific target pressures were evaluated with a McNemar test (Siegel 1956).

Results

Patients

We enrolled 32 subjects in the study. One subject discontinued early because she became pregnant. Two were removed from a treatment period early, one due to a lack of efficacy (timolol maleate and brimonidine treatment) and the other due to corneal epitheliopathy (fixed combination treatment). Both patients were advanced to the next period and morning trough measurements were obtained. However, in the epitheliopathy patient, the epitheliopathy recurred less severely on the timolol maleate and brimonidine treatment. Patient characteristics are listed in Table 1.

Table 1. Patient characteristics.

Characteristic		
Age (years)		62 ± 11
Gender	Male	13
	Female	19
Ethnicity	White	16
	Black	16
Diagnosis	Ocular hypertension	14
	Primary open-angle glaucoma	18
Visual acuity (ETDRS units)	Right eye	0.07 ± 0.21
	Left eye	0.08 ± 0.21
Mean deviation (dB)	Right eye	− 3.0 ± 4.7
	Left eye	− 4.1 ± 6.1
Systemic diseases (greater than a 15% incidence)	Hypertension	17
	Hypercholesterolaemia	15
	Post menopausal	10
	Diabetes	8
	Headaches	7
	Osteoarthritis	7
	Gastric reflux	6
	Depression	5

Intraocular pressure

The diurnal curve IOP measurements for the study are shown in Table 2 and Fig. 1. At each time-point, both the fixed combination and brimonidine 0.2% provided a statistical reduction in IOP from baseline (timolol maleate alone twice daily) and for the diurnal curve. When treatment groups were compared to each other, there was no statistical difference between the groups at morning trough (08 : 00) and at 2 and 4 hours after dosing. Following these time-points there was a trend, after the Bonferroni adjustment, to a greater reduction in IOP for the fixed combination over the brimonidine and timolol maleate concomitant therapy at each time-point ($p > 0.0078$). The greatest difference between groups was seen at the 12-hour evening trough at 20 : 00 hours (2.3 mmHg). However, the diurnal curve between treatment groups was significant by both a paired *t*-test ($p = 0.02$) and by a repeated measures of analysis ($p = 0.007$). In addition, a trend towards a greater number of patients reaching specific IOP target levels was observed with the fixed combination therapy (Table 2).

Table 2. Mean diurnal intraocular pressures (± standard deviation) ($n = 31$ trough, 29 other time-points).

Time (hours)	Baseline (mmHg)	Timolol maleate/ latanoprost fixed combination	Brimonidine and timolol maleate twice daily	p-values
Trough	23.0 ± 2.7	19.6 ± 4.6	20.4 ± 4.0	0.36
2	21.7 ± 3.2	18.8 ± 4.3	18.3 ± 2.7	0.50
4	21.4 ± 3.2	17.9 ± 3.8	18.8 ± 2.4	0.12
6	19.6 ± 3.7	17.3 ± 2.8	18.5 ± 2.8	0.04
8	20.1 ± 3.5	16.8 ± 2.9	18.7 ± 2.6	< 0.02
10	20.1 ± 3.3	17.7 ± 3.7	18.8 ± 2.7	0.05
12	20.2 ± 3.9	16.8 ± 3.6	19.1 ± 2.4	< 0.01
Diurnal	20.9 ± 2.8	17.9 ± 3.2	19.0 ± 2.4	0.02
≤ 16 mmHg*	1	9	4	0.06
≤ 17 mmHg*	1	13	5	0.14
≤ 18 mmHg*	5	15	9	0.08
≤ 21 mmHg*	17	23	22	> 0.9999

* Diurnal pressure, number of subjects

Adverse events

Adverse events are shown in Table 3. There was no statistical difference in the total number of adverse events, or for any individual adverse events, between treatment groups. Twenty-two events were observed in the fixed combination group and 24 in the brimonidine and timolol maleate group ($p > 0.05$).

The solicited symptom surveys showed no differences between treatments, nor from baseline, for all solicited questions including ocular effects of: dry eye, photophobia, blurred vision, tearing, burning on instillation, crusting of the eyelid, itching, sandy/gritty feeling, deep pain and constant irritation; or systemic effects including: fatigue, dizziness, despondency, depression and dry mouth.

Discussion

The timolol maleate/latanoprost fixed combination has been under development by Pharmacia, Inc. (Peapack, New Jersey, USA) for the past several years. Morning dosing of the fixed combination has been evaluated in several multicentre studies in Europe and the USA. A German study showed that the fixed combination reduced IOP further than timolol maleate alone by 1.9 mmHg and further than latanoprost alone by 1.2 mmHg (Pfeiffer 2000). In the USA, the fixed combination

Table 3. Adverse events (greater than an incidence of one).

Side-effect	Timolol maleate/ latanoprost fixed combination	Brimonidine and timolol maleate twice daily
Burning	5	2
Conjunctival hyperaemia	2	3
Ocular itching	2	2
Tearing	2	2
Dry eye	2	2
Eyelid laxity	2	1
Blurred vision	1	2
Floaters	1	1
Blepharitis	1	1
Diplopia	1	1
Photophobia	1	1
Soreness	1	1
Sinus allergies	1	1
Total	22	24

reduced IOP further than timolol maleate alone by 2.9 mmHg and further than latanoprost alone by 1.1 mmHg (Higginbotham et al. 2002). The fixed combination became available in the 2001 calendar year.

The reason for the relative lack of efficacy of the fixed combination over and above latanoprost alone in regulatory trials has not been explained completely. However, it may be, at least in part, because the fixed combination, which allows for once daily dosing of timolol maleate, was compared to timolol maleate dosed twice daily. In addition, the fixed combination was instilled in the morning whereas latanoprost alone was dosed in the evening. Previous data demonstrated that nighttime dosing lowered daytime pressures by about 1 mmHg (Alm & Stjernschantz 1995).

In this current trial we evaluated the efficacy and safety of the fixed combination product, dosed each evening, versus that of timolol maleate 0.5% and brimonidine 0.2%, which are commonly used as monotherapy and early adjunctive agents in primary open-angle glaucoma or ocular hypertension patients.

This study found that both the fixed combination treatment as well as timolol maleate and brimonidine concomitant therapy statistically reduced IOP from baseline on timolol maleate at every time-point and for the diurnal curve over the daytime and evening 12 hours. When treatment groups were compared directly, the diurnal curve IOPs for the fixed combination showed a greater statistical reduction in IOP than those for timolol maleate and brimonidine used together.

When both treatments were evaluated at 08 : 00 and 2 and 4 hours after dosing, they were statistically equal. However, there was a trend towards greater efficacy for the fixed combination at trough and 4 hours through 12 hours after dosing (after a Bonferroni correction). The greatest difference between the two treatments was observed at 12 hours (20 : 00 hours) after morning dosing, when there was a 2.3 mmHg difference between medicines.

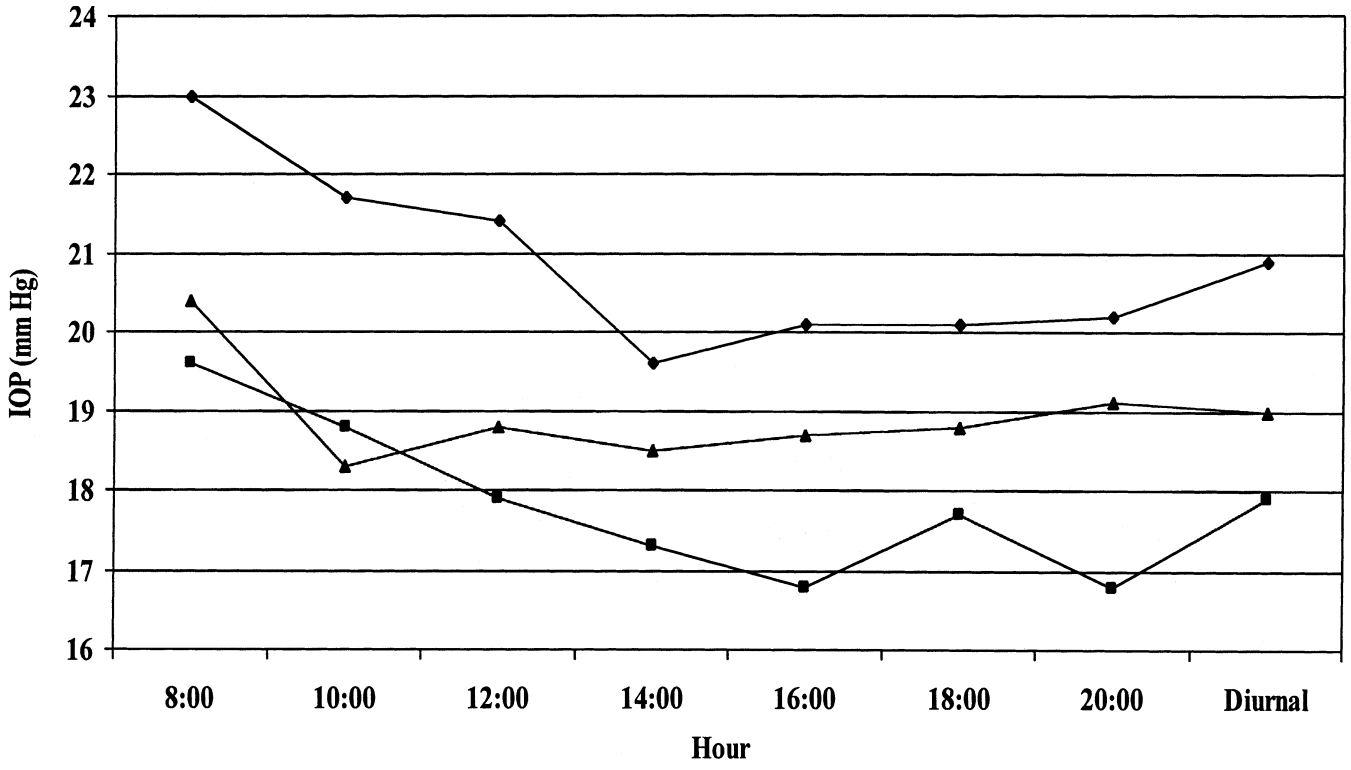

Fig. 1. Diurnal IOPs at baselines (timolol maleate only, diamonds) versus treatment with the timolol maleate/latanoprost fixed combination (squares) versus treatment with brimonidine and timolol maleate twice daily (triangles).

The reason for the diurnal difference between treatments in this study is not completely clear. However, it might be explained potentially by the trend towards a difference between groups at the late afternoon time-points. Past data published by Stewart et al. (2000) showed that by 10 hours after dosing with brimonidine as monotherapy, IOP returned to baseline; Konstas et al. (2001) demonstrated that brimonidine administered twice daily in the late afternoon and night-time hours elevated pressures by approximately 2 mmHg compared to three times daily dosing. However, unlike monotherapy, in this current study brimonidine administered twice daily provided a statistical reduction from baseline for 12 hours after dosing when used adjunctively with timolol maleate.

There was no statistical difference in the overall number of adverse events, or in individual adverse events, between treatment groups. One patient was discontinued because she became pregnant. Another was advanced to the next period because of corneal epitheliopathy (fixed combination treatment). This event recurred, however, although less severely, with timolol maleate and brimonidine concomitant therapy. The symptom surveys showed no difference between active treatments or from baseline for any ocular or systemic question.

Conclusion

This study suggests that the mean daytime diurnal IOP is reduced more with the timolol maleate/latanoprost fixed combination given in the evening than with brimonidine and timolol given concomitantly twice daily.

This study did not evaluate the TLFC with morning dosing versus timolol maleate and brimonidine. It is possible that the labelling on the fixed combination will instruct morning dosing as the regulatory trials dosed the product in this manner. In addition, this study did not evaluate the night-time diurnal curve of these two medicines, which potentially could have shown different results.

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