Eye (2004) 18, 1264–1269

www.nature.com/eye

CLINICAL STUDY

Daytime diurnal curve comparison between the fixed combinations of latanoprost 0.005%/ timolol maleate 0.5% and dorzolamide 2%/ timolol maleate 0.5%

AGP Konstas[1], VP Kozobolis[2], N Lallos[1], E Christodoulakis[3], JA Stewart[4] and WC Stewart[4,5]

[1]University Department of Ophthalmology AHEPA Hospital Thessaloniki, Greece

[2]Department of Ophthalmology University of Thrace University Hospital of Alexandroupolis Greece

[3]Glaucoma Unit Department of Ophthalmology University Hospital of Heraklion Crete, Greece

[4]Pharmaceutical Research Network, LLC Charleston, SC, USA

[5]University of South Carolina Medical School Columbia, SC, USA

Correspondence: WC Stewart Pharmaceutical Research Network, LLC 1639 Tatum Street Charleston SC 29412-2462, USA Tel: +1 843 762 6500 Fax: +1 843 762 7444 E-mail: prnc@bellsouth.net

Received: 2 July 2003 Accepted: 29 December 2003 Published online: 25 June 2004

Abstract

Purpose **The diurnal efficacy and safety of the fixed combinations of latanoprost/timolol given once daily *vs* dorzolamide/timolol given twice daily in primary open-angle glaucoma or ocular hypertensive patients.**

Design **A double-masked, two-centre, crossover comparison.**

Results **In 33 patients, the mean diurnal IOP (0800–2000, measured every 2 h) for latanoprost/ timolol fixed combination was 17.3 ± 2.2 mmHg and for dorzolamide/timolol, the fixed combination was 17.0 ± 2.0 mmHg ($P = 0.36$). Additionally, there was no statistical difference for individual time points following a Bonferroni correction. A bitter taste was found more frequently with the dorzolamide/timolol fixed combination ($n = 6$) than the latanoprost/ timolol fixed combination ($n = 0$) ($P = 0.040$), while the latanoprost/timolol fixed combination demonstrated more conjunctival hyperaemia ($n = 9$) than the dorzolamide/timolol fixed combination ($n = 2$) ($P = 0.045$). One patient was discontinued early from the dorzolamide/ timolol fixed combination due to elevated IOP.**

Conclusion **This study suggests that the daytime diurnal IOP is not statistically different between the dorzolamide/timolol fixed combination and latanoprost/timolol fixed combination in primary open-angle glaucoma and ocular hypertensive patients.**

Eye (2004) **18,** 1264–1269. doi:10.1038/sj.eye.6701446 Published online 25 June 2004

Keywords: latanoprost/timolol; dorzolamide/ timolol

Introduction

The latanoprost 0. 005%/timolol maleate 0.5% fixed combination (Xalacom®) was recently commercially released by Pfizer, Inc. Morning dosing of the fixed combination has been evaluated in several multi-centre studies in Europe and the United States. In Germany, Pfeiffer has shown that the fixed combination reduced the intraocular pressure further compared to timolol maleate alone by 1.9 mmHg, and from latanoprost alone by 1.2 mmHg.[1] In the United States, Higginbotham *et al*[2] demonstrated that the fixed combination reduced the intraocular pressure compared to timolol maleate alone by 2.9 mmHg and to latanoprost alone by 1.1 mmHg.

Compared to other adjunctive treatments, Stewart *et al*[3] have noted that the latanoprost 0.005%/timolol maleate 0.5% fixed combination was more effective at 6–12 h after dosing, and at the end of the daytime diurnal curve than brimonidine 0.2% and timolol maleate 0.5%. Feldman and coworkers showed that the latanoprost/timolol maleate fixed combination demonstrated 1 mmHg further pressure reduction using a three-point daytime diurnal curve than the dorzolamide 2%/timolol maleate 0.5% fixed combination (Feldman RM, ARVO

Abstract #295, 2002). However, unlike the study comparing the latanoprost/timolol maleate fixed combination to brimonidine and timolol, the number of time points evaluated in the Feldman study was limited. Consequently, the daytime characteristics of the ocular hypotensive efficacy between these two products remain incompletely described.

In this current trial, we have evaluated more extensively the daytime diurnal curve efficacy and safety of the latanoprost 0.005%/timolol maleate 0.5% fixed combination product, dosed each morning, *vs* the dorzolamide 2%/timolol maleate 0.5% fixed combination given twice daily in primary open-angle glaucoma or ocular hypertensive patients.

Materials and methods

Patients

Patients selected for this prospective study were recruited from the glaucoma clinic of the University Department of Ophthalmology, AHEPA Hospital, Thessaloniki, Greece and the outpatient clinic of the Glaucoma Unit, Department of Ophthalmology, University Hospital of Heraklion, Crete, Greece. We enrolled patients of either gender, older than 39 years of age, who demonstrated willingness to comply with the investigator's and protocol's instructions and to sign the Institutional Review Board approved informed consent document.

Patients who had a clinical diagnosis of primary open-angle or pigment dispersion glaucoma, or ocular hypertension in at least one eye (study eye) were included. Also, patients at screening should have demonstrated an intraocular pressure considered to be safe, in the study eye(s), in such a way as to assure clinical stability of vision and the optic nerve throughout the trial and have an intraocular pressure of 20–32 mmHg inclusive at the baseline 0800 measurement (Visit 2) after dosing with timolol the evening before in the study eye(s).

The patient exclusion criteria are listed in Table 1.

Table 1 Exclusion criteria

Unreliable applanation tonometry
Inadequate visualization of the ocular fundus or anterior chamber
Concurrent infectious/noninfectious conjunctivitis, keratitis, or uveitis
History of hypersensitivity to any components of the preparations used in this trial
History of hypersensitivity to any components of the preparations used in this trial
Childbearing potential or not using reliable birth control
Pregnancy or lactation
Clinically severe medical or psychiatric condition
Participation (or current participation) in any investigational drug or device trial within the previous 30 days prior to the screening visit
Intraocular conventional surgery or laser surgery within the past 2 months
Risk for uveitis or cystoid macular odema in this trial
Bronchial asthma, history of reactive airway, sinus bradycardia, second-or third-degree atrioventricular block, overt cardiac failure
Allergy to sulfa
History of ocular herpes simplex

Methods

All patients signed an Institutional Review Board approved informed consent agreement before any procedures were performed. At Visit 1, subjects had an ophthalmic and systemic history taken and had dilated funduscopy and automated visual field perimetry performed (Humphrey 24-2 or equivalent test). At this visit, as well as all other visits, the intraocular pressure was measured and Snellen visual acuity and slit-lamp biomicroscopy were performed. Qualified patients were then placed on timolol maleate 0.5% at 0800 and 2000 hours and asked to return in 4 weeks for the baseline visit (Visit 2).

At Visit 2, and at all other diurnal curve visits (Visits 4, 5, and 7), patients had intraocular pressure measurements at 0800, 1000, 1200, 1400, 1600, 1800, and 2000 hours. The morning study dose was instilled following the 08 00 measurement at this visit and at each diurnal curve visit. Patients who fulfilled the intraocular pressure inclusion requirements were randomly assigned to receive either the latanoprost 0.005%/timolol maleate 0.5% fixed combination once every morning (0800) and placebo once every evening (2000) or the dorzolamide 2%/timolol maleate 0.5% fixed combination twice daily (0800 and 2000) for the first 8-week treatment period.

A safety evaluation was performed after 2 weeks of treatment (Visit 3). At the end of Period 1, a diurnal curve was again performed (Visit 4). Patients were then treated again with timolol maleate 0.5% twice daily for 8 weeks and returned to clinic for the second baseline visit and diurnal curve (Visit 5). At this visit patients were placed on the second study medicine for Period II. A safety visit was again performed after 2 weeks of treatment (Visit 6) and a diurnal curve was performed at the end of the second 8-week treatment period (Visit 7).

The same investigator at each site measured the intraocular pressure and used the same calibrated instruments (Goldmann applanation tonometer) to perform diurnal curves of the intraocular pressure. During the study the investigator, staff, and patients

were masked to the treatment regimen. At each visit, local and systemic side effects that occurred during the treatment period were recorded.

Statistics

Statistical analyses comparing the intraocular pressure responses to the drug regimens were performed using a paired *t*-test for both individual time points and the entire diurnal curve (average mean pressures measured throughout the day).[4–7] The data were also evaluated by repeated measures of analysis. The significance level was set at 5% and a two-way analysis was used for all tests. This study had an 80% power to identify a 1.5 mmHg difference between individual time points and between mean diurnal pressures assuming a standard deviation of 2.8 mmHg between treatments.[8–11] An average eye intent-to-treat analysis was used. A Bonferroni correction was used to adjust the significance levels for individual time points. Adverse events were evaluated by a McNemar test.[12]

Results

Patients

A total of 33 patients were enrolled in this study; 33 completed at least all trough evaluations and 32 completed all time points in this study. One patient discontinued a treatment period early because the intraocular pressure was too high on the dorzolamide based fixed combination. All 33 patients were Caucasian. In all, 13 were male and 20 female with an average age of 64.5 ± 12.7 years. Five patients had ocular hypertension, 25 had primary open-angle glaucoma, and three had pigmentary glaucoma.

Intraocular pressure

This study found that the mean diurnal intraocular pressure for patients treated with the latanoprost 0.005%/timolol. maleate 0.5% fixed combination was 17.3 ± 2.2 mmHg and 17.0 ± 2.0 mmHg for the dorzolamide 2%/timolol maleate 0.5% fixed combination both by Student's *t*-tests ($P = 0.36$) and repeated measures of analysis ($P = 0.61$). The mean intraocular pressures at each time point are provided in Table 2 and diagramed in Figure 1. Both the latanoprost- and dorzolamide- based fixed combinations showed no statistical difference in intraocular pressure for the diurnal curve or at the individual time points following the Bonferroni correction. There was a trend at 1000 and 1200 hours of the dorzolamide 2%/timolol maleate 0.5% fixed combination to show a greater intraocular pressure reduction than the latanoprost 0.005%/timolol maleate 0.5% fixed combination ($P = 0.04$ and 0.03, respectively).

Both the fixed combinations provided a greater reduction of intraocular pressure at each time point compared to the timolol maleate twice-daily run-in. In addition, the reduction of intraocular pressure (Table 2) was statistically equal between groups at each time point and for the diurnal curve ($P > 0.05$).

Table 2 Mean diurnal intraocular pressures (mmHg ± SD)

Time (hours)	*n*	*Run-in*	*LTFC*	*Run-in*	*DTFC*	*Difference*	*P-value*
0800	33	22.1 ± 1.8	18.9 ± 2.4	22.2 ± 1.4	19.0 ± 1.9	0.03	0.92
1000	32	20.7 ± 2.4	17.8 ± 2.5	20.7 ± 2.6	17.3 ± 1.9	−0.59	0.04
1200	32	19.7 ± 2.3	17.5 ± 2.7	19.5 ± 2.2	16.7 ± 2.2	−0.84	0.03
1400	32	18.8 ± 2.4	16.7 ± 2.7	19.1 ± 2.6	16.0 ± 2.6	−0.66	0.12
1600	32	19.6 ± 2.7	16.6 ± 2.6	20.1 ± 2.9	16.5 ± 2.8	−0.05	0.91
1800	32	19.4 ± 2.1	16.6 ± 2.0	19.5 ± 2.3	16.7 ± 2.4	0.08	0.82
2000	32	20.5 ± 2.6	17.2 ± 2.0	20.5 ± 2.5	17.3 ± 2.1	0.14	0.71
Diurnal	32	20.1 ± 2.0	17.3 ± 2.2	20.2 ± 1.9	17.0 ± 2.0	−0.27	0.36
Reduction							
0800	33		3.1 ± 2.1		3.2 ± 1.6		0.77
1000	32		2.9 ± 2.1		3.5 ± 2.4		0.14
1200	32		2.2 ± 2.2		2.9 ± 2.1		0.11
1400	32		2.2 ± 1.9		3.1 ± 2.9		0.07
1600	32		3.0 ± 2.0		3.5 ± 2.5		0.26
1800	32		2.8 ± 1.9		2.8 ± 2.2		1.00
2000	32		3.3 ± 2.4		2.9 ± 2.0		0.51
Diurnal	32		2.8 ± 1.5		3.2 ± 1.6		0.26

LTFC, latanoprost 0.005%/timolol maleate 0.5% fixed combination.
DTFC, dorzolamide 2%/timolol maleate 0.5% fixed combination.

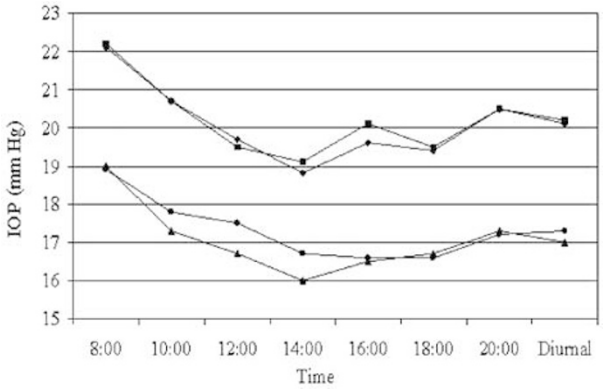

Figure 1 Mean diurnal intraocular pressures for the latanoprost/timolol fixed combination (circles) and run-in (diamonds) and the dorzolamide/timolol fixed combination (triangles) and run-in (squares).

Table 3 Adverse events (number of patients)

Event	*LTFC*	*DTFC*	*P-value*
Conjunctival hyperaemia	9	2	0.045
Burning/stinging on instillation	1	6	0.13
Bitter taste	0	6	0.04
Itchiness	5	0	0.07
Vision reduction	3	0	0.25
Lid erythema	2	0	0.48
Superficial punctate epitheliopathy	0	2	0.48
Watering	2	0	0.48

LTFC, latanoprost 0.005%/timolol maleate 0.5% fixed combination.
DTFC, dorzolamide 2%/timolol maleate 0.5% fixed combination.

Safety

Adverse events for this study are shown in Table 3. There were no statistically significant differences in adverse events between groups except that latanoprost-based fixed combination demonstrated more conjunctival hyperaemia ($P = 0.045$) and the dorzolamide based fixed combination demonstrated more taste perversion ($P = 0.040$).

Discussion

A fixed combination of dorzolamide 2%/timolol maleate 0. 5% (Cosopt®, Merck, Blue Bell, PA, USA) has been released commercially.[13] The dorzolamide 2%/timolol maleate 0.5% fixed combination is prescribed for twice daily dosing.[13] Clineschmidt *et al*[14] found in 102 patients with disease inadequately controlled on timolol alone that this fixed combination product further reduced the intraocular pressure by 1.1 mmHg from baseline at trough and resulted in a 2.8 mmHg decrease at peak (2 h after dosing). Hutzelmann *et al*[15] have shown that both the combination product and the addition of dorzolamide to timolol as a separate agent provided a 16.3% further decrease in intraocular pressure over timolol alone at trough and 21.8 and 21.6% reductions at peak, respectively. Boyle *et al*[16] have found that at trough the fixed combination product reduced intraocular pressure by 7.7 mmHg (27.4%) compared with 4.6 mmHg for dorzolamide and 6.4 mmHg for timolol alone (15.5 and 22.2%, respectively) from untreated baseline.

Fechtner and associates have evaluated daytime pressures of latanoprost 0.005% dosed each evening *vs* dorzolamide 2%/timolol maleate 0.5% fixed combination and showed that the intraocular pressure control was similar throughout the daytime diurnal curve with both these products (Fechtner *et al*, Invest Ophthalmol Vis Sci 1999;40:S665). More recently, Konstas *et al*[17] evaluated 24-h dosing of latanoprost every evening *vs* the dorzolamide 2%/timolol maleate 0.5% fixed combination and found, as did Fechtner and associates, that the daytime pressures were equal between medicines. However, in the evening (2200 hours) there was an efficacy advantage of the fixed combination compared to latanoprost. Stewart and associates also have found a similar reduction in pressure during the daytime between the dorzolamide 2%/timolol maleate 0.5% fixed combination and bimatoprost 0.03% dosed each evening (Internal data, Pharmaceutical Research Network, LLC).

The purpose of this trial was to evaluate the daytime diurnal intraocular pressure control and safety of the latanoprost 0.005%/timolol maleate 0.5% fixed combination given each morning *vs* the dorzolamide 2%/timolol maleate 0.5% fixed combination given twice daily.

This study showed that both the fixed combinations statistically reduced the intraocular pressure from timolol maleate monotherapy for the diurnal curve and at each time point. No differences were observed between groups for the intraocular pressure reduction.

For absolute pressure levels a statistical difference between groups was not observed for the diurnal curve individual time points. Also, there were no statistical differences following the Bonferroni correction. However, there was a trend at 1000 and 1200 hours for a greater reduction with the dorzolamide-based fixed combination.

The Feldman study, at 0800 and 1600 hours and over the 3-point diurnal curve demonstrated a greater reduction with the latanoprost-based *vs* the dorzolamide-based fixed combination (Feldman RM, ARVO Abstract #295, 2002). In contrast, the current study showed statistically similar pressures between these preparations at the 0800 and 1600 time points and across a 7-point diurnal curve. The reasons for the differences between

these studies are not completely known. In both studies, the latanoprost 0.005%/timolol maleate 0.5% fixed combination was dosed in the morning as indicated on the product label. However, a difference in the population sample existed between our studies. Feldman's study was carried out in the United States and included a more diverse ethnic population compared to the current study that took place in Greece. It is unknown if such an ethnic difference could influence the results of a glaucoma trial.

Safety was similar between the treatment groups. There were no statistically significant differences in adverse events between groups, except that the latanoprost based fixed combination demonstrated more conjunctival hyperemia ($P = 0.045$) and the dorzolamide-based fixed combination demonstrated more taste perversion ($P = 0.040$). Both these are known side effects with these medications.[14,16,18–20] One patient discontinued a treatment period early because the intraocular pressure was too high on the dorzolamide based fixed combination.

This study suggests that the daytime diurnal intraocular pressures are not statistically different between the latanoprost 0.005%/timolol maleate 0.5% fixed combination compared to the dorzolamide 2%/timolol maleate 0.5% fixed combination in primary open-angle glaucoma and ocular hypertensive patients.

More research is needed to understand fully the efficacy differences between these two products. This study did not evaluate the latanoprost based fixed combination dosed at night. Several previous studies have indicated that latanoprost dosed in the evening provided better daytime pressures than when dosed in the morning, which provides better night-time pressures.[17,20,21] Night-time dosing of the latanoprost based fixed combination could have improved the daytime pressure with the latanoprost based fixed combination.

References

1 Pfeiffer N. A comparison of the fixed combination of latanoprost and timolol with IST individual components in patients with glaucoma or ocular hypertension. The German Latanoprost Fixed Combination Study Group. *Invest Ophthalmol Vis Sci* 2001; **41** (Suppl): S754.
2 Higginbotham EJ, Feldman R, Stiles M, Dubiner H. Latanoprost and timolol combination therapy *vs* monotherapy: 1-year randomized trial. *Arch Ophthalmol* 2002; **120**(7): 915–922.
3 Stewart WC, Stewart JA, Day DG, Sharpe ED. Efficacy and safety of timolol maleate/latanoprost fixed combination *vs* timolol maleate and brimonidine given twice daily. *Acta Ophthalmol Scand* 2003; **81**(3): 242–246.
4 Book SA. *Essentials of Statistics*. McGraw Hill Book Company: New York, 1978, pp 117–122, 205-215.
5 Konstas AGP, Mantziris DA, Cate EA, Stewart WC. Effect of timolol on the diurnal intraocular pressure in exfoliation and primary open-angle glaucoma. *Arch Ophthalmol* 1997; **115**(8): 975–979.
6 Konstas AGP, Mantziris DA, Stewart WC. Diurnal intraocular pressure in untreated exfoliation and primary open-angle glaucoma. *Arch Ophthalmol* 1997; **115**(2): 182–185.
7 Orzalesi N, Rossetti I, Bottoli A, Invernizzi T, Fumagalli E, Fogagnolo P. Comparison of latanoprost, brimonidine and a fixed combination of timolol and dorzolamide on circadian intraocular pressure in patients with primary open-angle glaucoma and ocular hypertension. *Acta Ophthalmol Scand Suppl* 2002; **236**: 55.
8 Duff GR. A double-masked crossover study comparing the effects of carteolol 1 and 2% on intra-ocular pressure. *Acta Ophthalmol (Copenh)* 1987; **65**(5): 618–621.
9 Konstas AG, Lake S, Maltezos AC, Holmes KT, Stewart WC. Twenty-four hour intraocular pressure reduction with latanoprost compared with pilocarpine as third-line therapy in exfoliation glaucoma. *Eye* 2001; **154** (Part 1): 59–62.
10 Mundorf TK, Cate EA, Sine CS, Otero DW, Stewart JA, Stewart WC. The safety and efficacy of switching timolol maleate 0.5% solution to timolol hemihydrate 0.5% solution given twice daily. *J Ocular Pharmacol Ther* 1998; **14**: 129–135.
11 Stewart WC, Day DG, Stewart JA, Schuhr J, Latham KE. The efficacy and safety of latanoprost 0.005% once daily versus brimonidine 0.2% twice daily in open-angle glaucoma or ocular hypertension. *Am J Ophthalmol* 2001; **131**(5): 631–635.
12 Siegel S. *Nonparametric Statistics for the Behavioral Sciences*. McGraw-Hill Book Company: New York, 1956, pp 63–67.
13 Stewart WC. Perspectives in the medical treatment of glaucoma. *Curr Opin Ophthalmol* 1999; **10**: 99–108.
14 Clineschmidt CM, Williams RD, Snyder E, Adamsons IA. A randomized trial in patients inadequately controlled on timolol alone comparing the dorzolamide-timolol combination to monotherapy with timolol or dorzolamide. *Ophthalmology* 1999; **106** (12 Suppl): 17–24.
15 Hutzelmann J, Owens S, Shedden A, Adamsons I, Vargas E. Comparison of the safety and efficacy of the fixed combination of dorzolamide/timolol and the concomitant administration of dorzolamide and timolol: a clinical equivalence study. International Clinical Equivalence Study Group. *Br J Ophthalmol* 1998; **82**(11): 1249–1253.
16 Boyle JE, Ghosh K, Gieser DK, Adamsons IA. A randomized trial comparing the dorzolamide-timolol combination given twice daily to monotherapy with timolol or dorzolamide. *Ophthalmology* 1999; **106**(12 Suppl): 10–16.
17 Konstas AGP, Papapanos P, Tersis I, Houliara D, Stewart WC. 24-hour diurnal curve comparison of commercially available latanoprost 0.005% vs timolol/dorzolamide fixed combination. *Ophthalmology* 2003; **110**: 1357–1360.
18 Alm A, Stjernschantz J. Effects on intraocular pressure and side effects of 0.005% latanoprost applied once daily, evening or morning: a comparison with timolol. Scandinavian Latanoprost Study Group. *Ophthalmology* 1995; **102**(12): 1743–1752.
19 Camras CB. Comparison of latanoprost and timolol in patients with ocular hypertension and glaucoma: a 6-month masked, multicenter trial in the United States. The United States Latanoprost Study Group. *Ophthalmology* 1996; **103**(1): 138–147.

20 Watson P, Stjernschantz J. A six-month, randomized, double-masked study comparing latanoprost with timolol in open-angle glaucoma and ocular hypertension. The Latanoprost Study Group. *Ophthalmology* 1996; **103**(1): 126–137.

21 Konstas AG, Nakos E, Tersis I, Lallos NA, Leech JN, Stewart WC. A comparison of once-daily morning *vs* evening dosing of concomitant latanoprost/timolol. *Am J Ophthalmol* 2002; **133**(6): 753–757.