Comparison of daytime efficacy and safety of dorzolamide/timolol maleate fixed combination versus latanoprost

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PURPOSE. *To compare the 12-hour efficacy and safety of dorzolamide/timolol fixed combination (DTFC) dosed twice daily versus latanoprost dosed every evening following a timolol run-in in primary open-angle glaucoma patients.*
METHODS. *Following a 6-week timolol run-in patients were randomized to either DTFC or latanoprost for 6 weeks and then changed to the opposite treatment for 6 weeks. At the end of the run-in, and the end of each treatment period, the intraocular pressure (IOP) was measured every 2 hours between 8:00 AM and 8:00 PM.*
RESULTS. *Thirty-one patients completed at least one time point in both treatment periods. Both treatments reduced the IOP for the diurnal curve, and at each time point, from the timolol run-in baseline ($p<0.0001$). The 12-hour IOP on timolol was 22.1±2.8 mmHg, whereas on DTFC it was 18.1±2.8 and latanoprost 18.3±3.1 mmHg ($p=0.4$). Further, there was no statistical difference in IOP between treatments at any time point ($p\leq0.1$). There was no statistical difference for any individual adverse event between treatments ($p>0.05$).*
CONCLUSIONS. *This study suggests that following a timolol run-in both DTFC and latanoprost provide comparable daytime efficacy and safety. (Eur J Ophthalmol 2008; 18: 556-62)*

KEY WORDS. *Dorzolamide/timolol fixed combination, Latanoprost, Primary open-angle glaucoma*

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INTRODUCTION

Over the past three decades, timolol maleate has been the most common primary monotherapy agent used to treat primary open-angle glaucoma and ocular hypertension. Timolol remains a popular first line agent, especially in Europe, being used in this role approximately 30% of the time (1). However, latanoprost (Xalatan™, Pfizer, Inc., New York, NY, USA) was commercially released in 1996 as the first $F_2\alpha$ prostaglandin analog to reduce intraocular pressure (IOP). Since this time, latanoprost, and several newer prostaglandin analogs, have been used frequently as first line therapy, or as a change from timolol, when more IOP reduction was required (2-4).

The dorzolamide/timolol maleate fixed combination (Cosopt™, Merck & Co., Inc., Blue Bell, PA, USA) was introduced in 1998 and has been shown to increase ocular hypotensive efficacy over timolol alone (5-8). However, which one of these newer therapies, latanoprost or the dorzolamide/timolol fixed combination, is superior in IOP control and safety is not yet completely clear.

Fechtner and associates evaluated daytime IOP of latanoprost dosed each evening versus the dorzolamide/timolol fixed combination dosed twice daily and showed that control was similar with both these products (9). Further, Konstas and coworkers, as well as Orzalesi and as-

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sociates, found using 24-hour testing that the fixed combination and latanoprost provided clinically equivalent IOP lowering (10, 11). Nonetheless, the number of daytime time points evaluated in these studies was limited to four (9-11). In addition, these studies did not evaluate the change from timolol monotherapy as would be expected to occur frequently in clinical practice.

The purpose of this study was to compare the 12-hour diurnal efficacy, measured every 2 hours, and safety of the dorzolamide/timolol fixed combination dosed twice daily versus latanoprost dosed every evening following a timolol run-in in patients with primary open-angle glaucoma.

METHODS

Patients

Patients selected for this prospective study were recruited from two clinical sites in the United States. We enrolled patients who were 18 years of age or older; had a clinical diagnosis of primary open-angle glaucoma in at least one eye (study eye); had at screening an IOP considered safe, in the study eye(s), with assurance of clinical stability of vision and the optic nerve throughout the trial; had at baseline an IOP between 22 and 30 mmHg inclusive on timolol twice daily at the 8:00 AM measurement (Visit 2) and the pressure was ≤30 mmHg in both eyes at all time points; in eyes not included in the study the IOP was controlled on timolol monotherapy (during run-in) or the assigned study drug alone during the randomized active treatment periods; and Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity was 1.0 or better in each eye.

Patients were excluded from this study if they demonstrated any abnormality preventing reliable applanation tonometry in study eye(s); any opacity or uncooperativeness that restricted adequate examination of the ocular fundus or anterior chamber in the study eye; any concurrent infectious/noninfectious 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; and any clinically significant, serious, or severe medical or psychiatric condition, as well as women of childbearing potential not using reliable means of birth control or pregnant or lactating females. Patients who participated (or had current participation) in any investigational drug or device trial within the previous 30 days prior to Visit 1; had intraocular conventional surgery or laser surgery within the past 3 months; had risk of visual field or visual acuity worsening as a consequence of participation in the trial (according to the investigator's best judgment); were unable to understand the trial procedures; anticipated change in systemic hypertensive medications, had progressive retinal or optic nerve disease apart from glaucoma; were unwilling to accept the risk of iris or periocular skin color or eyelash changes; were at risk for uveitis or cystoid macular edema because of participation in this trial; had a history of allergy to sulfa, ocular herpes simplex, cystoid macular edema, or uveitis; or had bronchial asthma, history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, overt cardiac failure, or cardiogenic shock also were excluded.

Procedures

All patients signed an informed consent agreement approved by an independent institutional review board before any procedures were performed. At the screening examination at week –6 (Visit 1) patients who met the inclusion and exclusion criteria underwent ophthalmic and systemic history, gonioscopy, visual field assessment (Humphrey 24-2, Humphrey Field Analyzer, San Leandro, CA, USA), and dilated funduscopy. At each visit patients had their IOP measured by Goldmann applanation tonometry and ETDRS visual acuity performed, and underwent slit lamp biomicroscopy.

Qualified subjects were placed on timolol twice daily monotherapy and scheduled to return in 6 weeks for the Day 0 (Visit 2) baseline examinations. At this visit, following the 8:00 AM IOP measurement and the morning dose of timolol, patients with a qualifying IOP in at least one eye underwent diurnal curve testing, every 2 hours, for a 12-hour period (8:00 AM–8:00 PM).

Patients then were randomized to either the dorzolamide/timolol fixed combination given twice daily or latanoprost given each evening and placebo given each morning. The study medication was masked by placing a label over the commercially available medication bottle. The medicine was concealed further in an opaque medication bottle. Patients were instructed not to show any bottle to the study personnel (except a designated dosing coordinator) or the investigator.

Patients returned at the end of Period 1 (Week 6, Visit 3) for diurnal curve measurements including the 8:00 AM IOP and then every 2 hour diurnal pressures following the

morning dosing of the study medicine. Patients then were switched to the Period 2 masked medication. Patients returned again at Week 12 (Visit 4) for the end of Period 2 evaluations including diurnal pressure measurements. Patients were exited from the study barring any unresolved adverse events.

Statistics

The data were analyzed by PRN Pharmaceutical Research Network, LLC. All data analyses were two-sided and had an a-level of 0.05. The primary efficacy variable, the 12-hour diurnal IOP (average of the seven individual time points) difference between Visits 3 and 4, was analyzed by an ANOVA with repeated measures (12). This study provided approximately an 80% power that a 1.5 mmHg difference could be excluded between groups if 27 subjects completed the study. An intergroup standard deviation of 2.8 mmHg was assumed (13-16). An intent to treat, average eye analysis, was used.

The secondary efficacy variable, IOP at each time point, was analyzed by a paired *t*-test within the ANOVA model. Visual acuity for intergroup analysis was evaluated with a paired *t*-test. Adverse events were evaluated with a McNemar test. Funduscopy and visual fields were not statistically evaluated.

RESULTS

Patients

Thirty-one patients completed at least one time point in both treatment periods. The average age was 66.9 ± 10.2 years. Nine patients were male and 22 were female and 9 patients were African American and 22 Caucasian. The iris color was brown in 18 patients, blue in 8, hazel in 4, and green in 1 patient. All patients had primary open-angle glaucoma.

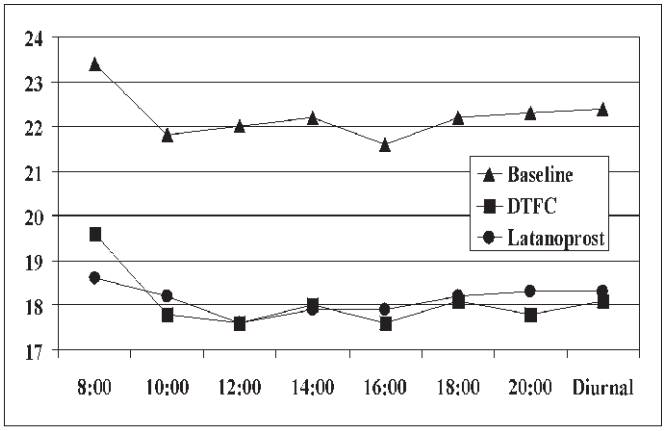

Fig. 1 - *Intraocular pressures for baseline (triangles), latanoprost (circles), and the dorzolamide/timolol maleate fixed combination (squares). DTFC= Dorzolamide/timolol fixed combination.*

Intraocular pressure

The absolute level of IOP results are shown in Table I and the reduction of the pressure from baseline in Table II. The IOP results are also diagramed in the Figure. Each study treatment caused a decrease in IOP for the mean diurnal curve as well as at each individual time point from the timolol-run in ($p<0.0001$). When the treatments were compared directly there was no statistical difference for the 12-hour diurnal average, or at any individual time point, of the absolute level of IOP, or of the reduction from baseline, between treatments ($p>0.05$).

TABLE I - MEAN DIURNAL INTRAOCULAR PRESSURES (mmHg ± Standard Deviation)

Time points	N	Baseline	DTFC	Latanoprost	p value
8:00 am	31	23.4±1.5	19.6±3.0	18.6±3.9	0.1
10:00 am	31	21.5±2.8	17.8±3.1	18.2±3.8	0.5
12:00 pm	30	22.0±2.9	17.6±2.9	17.6±3.3	1.0
2:00 pm	30	22.1±3.0	18.0±3.0	17.9±3.1	0.9
4:00 pm	31	21.6±3.9	17.7±3.3	17.9±3.7	0.8
6:00 pm	31	22.2±3.4	18.1±3.6	18.2±4.1	0.9
8:00 pm	31	22.3±3.5	17.8±3.8	18.3±3.9	0.3
12-hour	30	22.4±2.5	18.1±2.8	18.3±3.1	0.4

DTFC = Dorzolamide/timolol fixed combination

Adverse events

The most frequent ocular and systemic adverse events are shown in Table III. There were 7 reported events on latanoprost and 10 on the dorzolamide/timolol fixed combination. There was no statistical difference for any individual adverse event between treatments. There were no serious adverse events noted in this study. In addition, no patient discontinued treatment early. One patient missed two time points for the pressure measurements because of a scheduling problem.

DISCUSSION

Latanoprost is an $F_2\alpha$ prostaglandin analog which is highly selective for the FP-receptor (17). Several previous studies have indicated that latanoprost reduces the pressure by increasing uveoscleral outflow (18-21). When compared to timolol given twice daily, latanoprost once daily has demonstrated either an equal or statistically greater reduction in IOP (2-4). Further, latanoprost has been shown to have greater efficacy than several other commonly used glaucoma medicines, including brimonidine and dorzolamide, and has generally been shown to have a similar efficacy to the other newer prostaglandin analogs, travoprost and bimatoprost (22-26). Side effects associated with latanoprost have been iris color darkening, eyelash growth, and conjunctival hyperemia (27). A possible association to uveitis, recurrent corneal herpes keratitis and cystoid macular edema, also may exist in some patients (28-30).

In contrast, both components of the fixed combination of dorzolamide and timolol decrease aqueous production by separate, but additive, mechanisms (31, 32). Clineschmidt and coworkers found in patients inadequately controlled on timolol alone that fixed combination further reduced the IOP 1.1 mmHg from baseline at trough (6). Further, Boyle and coworkers have found that at trough the combination product reduced IOP 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 an untreated baseline (8). In contrast, Hutzelmann and associates showed that both the fixed combination and the ad-

TABLE II - REDUCTIONS IN PRESSURE FROM TIMOLOL RUN-IN BASELINE (mmHg ± Standard Deviation)

Time points	N	DTFC	Latanoprost	p value
8:00 am	31	3.9±2.9	4.8±3.8	0.1
10:00 am	31	4.0±2.8	3.6±3.6	0.5
12:00 pm	30	4.4±3.2	4.4±4.0	1.0
2:00 pm	30	4.1±3.6	4.2±3.5	0.9
4:00 pm	31	3.9±3.4	3.7±4.2	0.8
6:00 pm	31	4.2±3.1	4.1±3.8	0.9
8:00 pm	31	4.5±3.5	4.0±4.2	0.3
12-hour	30	4.2±2.5	4.1±3.3	0.7

DTFC = Dorzolamide/timolol fixed combination

TABLE III - SYSTEMIC AND OCULAR ADVERSE EVENTS

Adverse events	Latanoprost Period 1	DTFC Period 2	p value
Burning/stinging	0	5	0.07
Tearing	1	2	1.0
Blurred vision	1	2	1.0
Upper respiratory infection	2	0	0.5
Gallstones	1	0	1.0
Inflamed cuspid	1	0	1.0
Cough	1	0	1.0
Headache	0	1	1.0

DTFC = Dorzolamide/timolol fixed combination

dition of dorzolamide to timolol as a separate agent provided a 16.3% further decrease in IOP over timolol alone at trough (7). Common local side effects with the dorzolamide/timolol fixed combination have been mostly related to the dorzolamide component, including bitter taste and stinging/burning on instillation.

The purpose of this study was to compare the 12-hour diurnal efficacy, measured every 2 hours, and safety of the dorzolamide/timolol fixed combination dosed twice daily versus latanoprost dosed every evening following a timolol run-in in patients with primary open-angle glaucoma.

This study showed that both latanoprost and the dorzolamide/timolol fixed combination reduced the IOP from untreated baseline for the 12-hour pressure curve and at each individual time point. In addition, when both treatments were compared the 12-hour mean level of IOP was statistically and clinically equivalent between treatment groups and at individual time points. Further, similar findings between treatments were observed with the reduction of pressure as with the mean level of IOP.

Therefore, the extent of pressure reduction, from timolol monotherapy, was greater for both the fixed combination (4.2 mmHg) and latanoprost (4.1 mmHg) than might have been anticipated from prior studies. In the latanoprost regulatory trials the difference between this prostaglandin and timolol was generally less than 2 mmHg (32). In addition, the regulatory studies comparing the fixed topical dorzolamide/timolol fixed combination to timolol showed a difference of 1.2 mmHg between these products (33-35). The reason for the greater pressure reduction in the current study is not known precisely. However, there may have been an unusually greater number of timolol nonresponders in this study because of the higher qualifying pressure (22–30 mmHg) on the timolol monotherapy designed to demonstrate responsiveness to the study medicine. However, it is conceivable that this qualifying pressure may have selected out patients who were less responsive to timolol allowing for the greater reduction than anticipated with either of the study medicines.

In contrast, our findings comparing the two study treatments are consistent with prior studies by Fechtner and coworkers and Konstas and associates who found statistically similar daytime pressures between latanoprost and the dorzolamide/timolol fixed combination (8, 9, 36). This study differed marginally from the study by Orzalesi and coworkers, which found one daytime time point (9:00 AM) was lower with the fixed combination (11). However, it should be noted that in the work of Konstas and Stewart, some evidence of a lower evening pressure with the fixed combination has been observed (10) although this finding has not been consistent (36).

This study is additive to information from previous trials in several ways. First, this study had more time points between 8:00 AM and 8:00 PM measured at 2-hour intervals, which helped confirm the similarity of daytime pressures between the dorzolamide/timolol fixed combination and latanoprost. Second, this study had more patients with glaucoma (30 compared with 10) compared with the Orzalesi study and the current study also had a slightly longer follow-up (6 weeks versus 4 weeks), which may allow for the slightly more consistent results between products, especially because of the known long-term drift with timolol (11, 32). Finally, this study evaluated directly the decrease in IOP between these two treatments following a timolol run-in. When evaluated separately in previous studies, at limited diurnal measurements (two and three, respectively), Clineschmidt and associates demonstrated that the fixed combination provided 1.2 mmHg more pressure reduction from timolol and Camras and coworkers showed a further 1.5 mmHg reduction after patients treated with timolol were changed to latanoprost (3, 6).

Timolol remains a very common primary therapy for elevated IOP in the United States and especially in Europe. Consequently, these data may provide greater confidence to the physician that timolol-treated patients may be changed to either latanoprost or the dorzolamide/timolol fixed combination with similar improved daytime efficacy.

Regarding safety, there were no statistical differences for any individual adverse event between treatments and no serious adverse events noted in this study. Side effects were typical of those typically reported for these medications. In addition, no patients discontinued treatment early.

This study suggests that, following a timolol run-in, both the dorzolamide/timolol fixed combination and latanoprost provide comparable daytime efficacy and safety.

This study did not evaluate the mid or long-term results of latanoprost and the dorzolamide/timolol fixed combination. Konstas and coworkers recently described mid-term pressure reductions between these two compounds over 24 hours and found no difference between treatments in the longer term analysis (36). Long-term (1–2 years) data evaluating latanoprost and the dorzolamide/timolol fixed combination would be valuable. In addition, this study did not examine long-term visual outcomes to determine if one of the medicines has an advantage over the other on

visual results. Future research may further clarify the appropriate use of these medicines in the stepwise therapy of glaucoma.

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