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The efficacy and safety of timolol maleate versus brinzolamide each given twice daily added to travoprost in patients with ocular hypertension or primary open-angle glaucoma

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PURPOSE. *To compare the efficacy and safety of timolol maleate 0.5% versus brinzolamide 1% when added to travoprost 0.004% in patients with ocular hypertension or primary open-angle glaucoma.*
DESIGN. *A prospective, double-masked, randomized, active-controlled, parallel comparison.*
METHODS. *Qualified patients at Visit 1 were placed on travoprost dosed every evening for 4 weeks and then were randomized at baseline (Visit 2) to the addition of timolol maleate or brinzolamide each given twice daily. Patients returned to clinic at Week 4 (Visit 3) for a safety visit and Week 12 (Visit 4) for an efficacy visit. At Visits 2 and 4 the intraocular pressure (IOP) was measured at 08:00, 12:00, and 16:00 hours.*
RESULTS. *Ninety-seven patients on brinzolamide had a baseline diurnal IOP of 21.5±2.2 mmHg and 95 on timolol maleate had 21.3±2.5 mmHg, each added to travoprost. The diurnal mean IOP at Week 12 was 18.1±2.7 mmHg for brinzolamide and 18.1±3.0 mmHg for timolol maleate ($p=0.96$). There was no statistical difference found between treatment groups in the absolute level of pressure, or in the reduction in IOP from baseline, at each time point or for the diurnal curve ($p>0.05$). There was no significant difference for any adverse event between groups ($p>0.05$), with the most common side effect being conjunctival hyperemia in 15/97 (16%) brinzolamide and 6/95 (6%) timolol treated patients ($p=0.06$).*
CONCLUSIONS. *This study showed that brinzolamide provides similar safety and efficacy compared to timolol maleate when added to travoprost. (Eur J Ophthalmol 2006; 16: 816-23)*

KEY WORDS. *Timolol maleate, Brinzolamide, Travoprost, Ocular hypertension, Primary open-angle glaucoma*

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INTRODUCTION

Prostaglandin analogs first became available as ocular hypotensive agents in 1996. Because of their efficacy and relative safety, in many areas of the world they became the preferred first-line glaucoma treatment. Prior research has shown that a greater percentage of patients can be controlled with prostaglandin analogs compared to timolol maleate as a single agent (1-3).

Nonetheless, many patients still require adjunctive medication to control their intraocular pressure (IOP) to prevent glaucomatous progression. Several studies have evaluated additive therapy to latanoprost. Stewart and associates showed that once daily timolol maleate could be added to latanoprost with a 3 mmHg further IOP reduction after 24 hours (4). Stewart and coworkers also demonstrated that brimonidine could be added to latanoprost with equal efficacy to the latanoprost/timolol fixed combination (5). Konstas and associates noted that dorzolamide could be used with similar efficacy to brimonidine purite, each dosed twice daily, added to latanoprost (6).

Travoprost (Travatan®, Alcon, Inc., Fort Worth, TX, USA) is a newer prostaglandin analog that has shown a greater ocular hypotensive effect compared to timolol maleate and a similar efficacy to latanoprost (7). Orengo-Nania and coworkers have demonstrated that travoprost can be added to timolol with an additional 4 to 5 mmHg further IOP reduction (8). Limited data exist, however, that evaluate the additivity of other ocular hypotensive agents to travoprost specifically.

The purpose of this study is to compare the efficacy and safety of timolol maleate compared to brinzolamide each given twice daily when added to travoprost given each evening in patients with open-angle glaucoma or ocular hypertension.

MATERIALS AND METHODS

Design

The design of this study was a prospective, double-masked, randomized, active-controlled, parallel comparison with 10 investigators in eight countries.

Patients

Subjects must have fulfilled the following conditions to qualify for inclusion into the trial: 18 years of age or older; willing to comply with the investigator's and protocol's instructions; signed the Ethics Committee approved informed consent document; a clinical diagnosis of ocular hypertension, primary open-angle or pigment dispersion glaucoma in at least one eye (study eye); IOP considered to be safe, in both eyes, in such a way that assured clinical stability of vision and the optic nerve throughout the trial; in eyes not included in the study the IOP was controlled to a safe level on no pharmacologic therapy or study drugs only during the trial; treated with bimatoprost, latanoprost, or travoprost once daily as monotherapy for a minimum of 2 weeks at Visit 1 and an IOP of between 19 and 32 mmHg inclusive in at least one eye and ≤32 mmHg in both eyes; at Visit 2 (baseline), IOP between 19 and 32 mmHg inclusive at the 08:00 measurement in at least one eye and ≤32 mmHg at all time points in both eyes; or visual acuity of 6/60 or better in both eyes.

Patients with any of the following conditions at the time of initiating adjunctive therapy were not enrolled into the trial: presence of exfoliation syndrome or exfoliation glaucoma; any abnormality preventing reliable applanation tonometry in study eyes; any opacity or patient 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 (blepharitis or non-clinically significant conjunctival injection was allowed); any history of allergic hypersensitivity or poor tolerance to any components of the preparations used in this trial; women of childbearing potential not using reliable means of birth control; pregnant or lactating women; any clinically significant, serious, or 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 (Visit 1); intraocular conventional surgery or laser surgery within the past 3 months in the study eyes; according to the investigator's best judgment, risk of visual field or visual acuity worsening as a consequence of participation in the trial; inability to understand the trial procedures, and thus inability to give informed consent; any anticipated change in systemic hypotensive therapy during the active treatment portion of the trial (Visits 1–4) which might include adjustments to oral ß-adrenergic blockers, α-agonists and blockers, angiotensin converting enzyme inhibitors, and calcium channel blockers; progressive retinal or optic nerve dis-

ease from any cause; unwilling to accept the risk of iris color or eyelash changes; history of, or at risk for, uveitis or cystoid macular edema in this trial; history of ocular herpes simplex; contraindications to β-blocker therapy including reactive airway disease, secondary or third degree heart block, bradyarrhythmias, and uncontrolled heart failure; history of sulfa allergy; or Fuch's corneal dystrophy, moderate or severe guttata, or a subjectively low endothelial cell count by slit lamp biomicroscopy.

Procedures

All patients signed an Ethics Committee approved informed consent document before any procedures were performed. Patients who were being treated with bimatoprost, latanoprost, or travoprost monotherapy, and who had an IOP between 19 and 32 mmHg inclusive at 08:00 hours, underwent a screening examination at Week –4 (Visit 1). At the screening examination, and each subsequent visit, patients underwent slit lamp biomicroscopy, Goldmann applanation tonometry, and Snellen visual acuity measurements. At the screening examination only, patients underwent pachymetry, dilated funduscopy, and automated visual field testing (Humphrey 24-2, Humphrey Field Analyzer, Humphrey Instruments, San Leandro, CA, or similar automated perimeter and program). Patients who met the inclusion and exclusion criteria were switched from their current prostaglandin therapy to travoprost 0.004% dosed at each 20:00.

Patients then returned for the Day 0 (Visit 2) baseline examinations. Patients eligible for randomization had IOP between 19 and 32 mmHg inclusive at 08:00 on travoprost treatment. Patients then underwent baseline diurnal curve testing at 12:00 and 16:00 hours following the 08:00 IOP measurement. Patients were then randomized to either timolol maleate 0.5% or brinzolamide 1% (Azopt", Alcon, Fort Worth, TX) dosed twice daily in the study eyes added to the travoprost treatment. Masking was accomplished by using identical bottles, labels, and bottle caps so the physician, staff, and patients could not detect a difference between medicines. Travoprost therapy was open-label.

Patients returned at Week 4 (Visit 3) at 16:00 for an IOP measurement and safety evaluation. At Week 12 (Visit 4) patients had their 08:00 IOP measured. After morning dosing of the study medicine the efficacy diurnal curve was measured. Patients then were exited from the study barring any unresolved adverse events.

Statistics

The primary efficacy variable, mean diurnal IOP, was analyzed by a repeated measures of analysis test (9). A standard deviation of 3.5 mmHg was assumed. This study provided an 80% power that a 1.5 mmHg difference could be excluded between groups if at least 80 patients in each arm completed the study. A per-protocol, worst eye analysis was used. When both eyes had equal mean pressures then the right eye was chosen. A test of non-inferiority (alpha level 2.5%) was used to determine if brinzolamide was inferior to timolol maleate for the diurnal curve and for each individual mean pressure level. Secondary efficacy variables for the IOP were evaluated by a *t*-test within the analysis of variance test.

Age and pachymetry were evaluated by a Student *t*-test. Sex, study eye, and diagnosis were evaluated by a chi square test. Adverse events were evaluated using a chi square or Fisher exact test as appropriate (9). Adverse events were listed separately for ocular and systemic events. Funduscopy, visual field, and slit-lamp parameters were not statistically evaluated. Differences in response rates based on pachymetry were performed between each subgroup with a Student *t*-test for three ranges of corneal thickness: thin (0.452–0.540), medium (0.541–0.583), and thick (0.584–0.701). Each subgroup represents an approximate third of the patient population divided among the highest, mid-range, and lowest pachymetry values. Each site used whatever contact pachymeter was available to them.

Serious adverse events were listed with the investigator's assessment of its relationship to the study medicine. Discontinued patients (after Visit 2) were listed by the associated reason and study medicine. Analysis of discontinued patients between study groups was performed by a chi square test (9).

RESULTS

Patients

A total of 215 patients were placed on the travoprost run-in of which 100 patients were randomized to timolol maleate and 101 to brinzolamide at Visit 2. There were 14 screening failures at Visit 2. Of the randomized patients, 95 patients on timolol maleate and 97 patients on brinzolamide completed Visit 4 per the protocol specifications.

Of the nine patients who did not complete Visit 4, six patients were discontinued due to protocol violations, two brinzolamide-treated patients due to a case each of blurred vision and conjunctival hyperemia, and one timolol-treated patient due to palpitations, dizziness, and weakness.

Table I lists the patient characteristics for those who completed Visit 4. All patients were white. No statistical differences were noted between groups for any baseline characteristic.

Intraocular pressure

The mean IOP levels for each medicine at each visit are shown in Table II and Figure 1. There was no statistical difference found between medicines at baseline (Visit 2, p>0.20), the safety check (Visit 3, p=0.20), or active treatment (Visit 4, p=0.78) for the diurnal IOP and individual time points. The test of non-inferiority showed that brinzolamide was not inferior to timolol maleate for the diurnal curve and for each individual mean pressure level

TABLE I - BASELINE PATIENT CHARACTERISTICS

		Timolol maleate and travoprost	Brinzolamide and travoprost	p Value
Age, y, mean ± SD		62.2±10.4	63.9±11.7	0.29
Pachymetry, mm, mean ± SD		0.562±0.046	0.560±0.039	0.83
	Male	35	40	0.56
	Female	60	57	
Study eye	Right eye	5	3	0.70
	Left eye	6	5	
	Both eyes	84	89	
Diagnosis	Primary open-angle glaucoma	68	71	0.56
	Ocular hypertension	26	26	
	Pigmentary glaucoma	1	0	
Patient history (most common diagnoses)	Cataract	41	45	0.37
	Conjunctiva hyperemia	29	26	0.63
	Darker, longer lashes	8	16	0.13
	Hypertension	51	51	0.77
	Diabetes mellitus	21	17	0.47
	Osteoarthritis	11	10	0.82

TABLE II - INTRAOCULAR PRESSURE, mmHg, MEAN ± SD

	N	Timolol maleate and travoprost	N	Brinzolamide and travoprost	p Value
Screening IOP	95	22.6±3.0	97	22.6±2.7	0.92
Baseline 08:00	95	22.6±2.8	97	22.3±2.6	0.54
Baseline 12:00	95	20.9±2.6	97	21.2±2.6	0.35
Baseline 16:00	95	20.4±2.9	97	20.9±2.6	0.20
Baseline diurnal	95	21.3±2.5	97	21.5±2.2	0.53
Visit 3 16:00	95	17.6±2.9	97	18.1±2.7	0.20
Visit 4 08:00	95	19.2±3.6	97	19.2±3.3	0.97
Visit 4 12:00	95	17.7±3.3	97	17.6±2.8	0.84
Visit 4 16:00	95	17.4±3.3	97	17.6±3.0	0.78
Visit 4 diurnal	95	18.1±3.0	97	18.1±2.7	0.96

IOP = Intraocular pressure

TABLE III - REDUCTION OF INTRAOCULAR PRESSURE FROM TRAVOPROST MONOTHERAPY, mmHg, MEAN ± SD

	Timolol maleate and travoprost, n = 95	Percent reduction	Brinzolamide and travoprost, n = 97	Percent reduction	p value
08:00	3.4±3.0	6.6	3.2±2.8	7.0	0.54
12:00	3.1±2.8	6.7	3.6±2.7	5.9	0.26
16:00	3.0±3.1	6.8	3.4±2.7	6.1	0.36
Diurnal	3.2±2.4	6.7	3.4±2.1	6.3	0.55

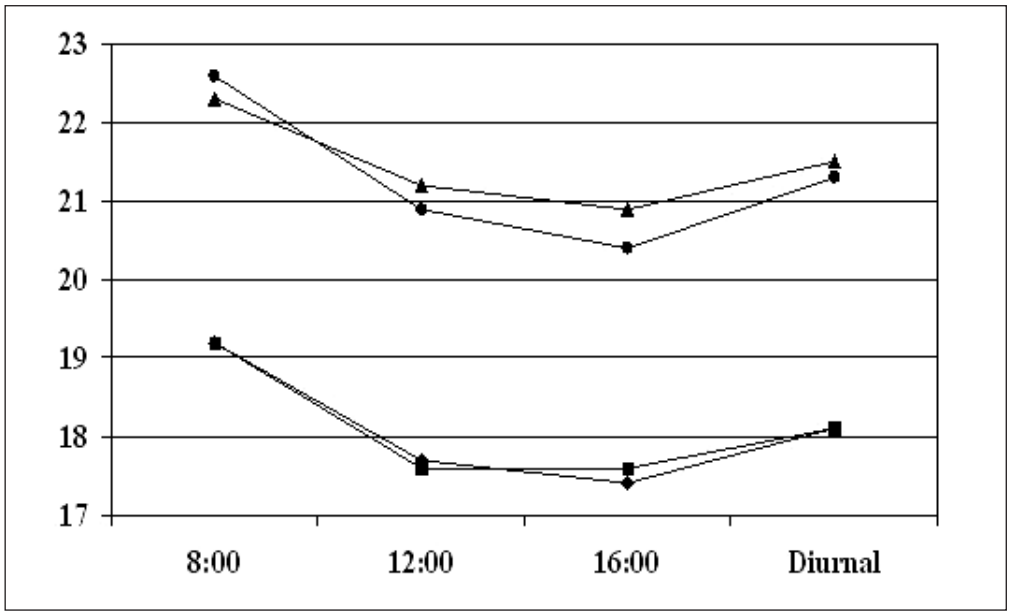

Fig. 1 - *Intraocular pressure comparison between timolol maleate (circles) and brinzolamide (triangles) at baseline and timolol maleate (diamonds) and brinzolamide (squares) at Visit 4.*

(p>0.05). No difference in the response of the study medicines was observed based on pachymetry for any of the three subgroups of corneal thickness (p>0.3). Also, there was no difference in the IOP response between treatment groups for the diurnal curve for ocular hypertension (brinzolamide n=26, 16.6±2.9 and timolol n=25, 17.5±2.1 mmHg, p=0.14) and primary open-angle glaucoma (brinzolamide n=71, 17.6±2.6 and timolol n=68, 17.9±3.0 mmHg, p=0.49) evaluated separately.

The reduction of IOP from baseline for each medicine is shown in Table III. Each medicine reduced the IOP at

TABLE IV - OCULAR ADVERSE EVENTS (two or more events)

	Timolol maleate and travoprost	Brinzolamide and travoprost	p value
Conjunctiva hyperemia	6	15	0.06
Ocular burning sensation	4	10	0.16
Longer lashes	7	6	0.78
Darker lashes	5	4	0.75
Decreased vision	2	4	0.68
Foreign body sensation	1	5	0.21
Ocular itching	1	3	0.32
Edema of the eyelids	0	2	0.50

TABLE V - SYSTEMIC ADVERSE EVENTS (two or more events)

	Timolol maleate and travoprost	Brinzolamide and travoprost	p value
Influenza	1	3	0.62
Dizziness	2	0	0.24
Weakness	2	0	0.24

each time point and for the diurnal curve from baseline ($p<0.05$). There was no statistical difference found between medicines for the diurnal IOP and individual time points ($p>0.26$).

Adverse events

The most frequent ocular adverse events are listed in Table IV. The total number of ocular adverse events for brinzolamide was 50 and 27 for timolol. Both medicines were well tolerated with the most common adverse event being conjunctival hyperemia (15/97, 16%) for brinzolamide and for timolol (6/95, 6%) ($p=0.06$). There was no statistically significant difference for any adverse event between groups ($p>0.05$).

Systemic adverse events were infrequent and there was no statistical difference between medicines for any specific event. The most frequent systemic adverse events are listed in Table V. The total number of systemic adverse events for brinzolamide was 8 and 13 for timolol.

Three serious adverse events occurred during the study. The first serious event was due to pneumonia while the patient was being treated with timolol. This patient was non-evaluable due to a protocol violation. The second serious adverse event was due to erysipelas while being treated with timolol. This patient continued in the study. The third patient had a B-12 deficiency while in the run-in period on travoprost treatment alone. The investigators did not believe that any of these events were associated with the study medicines or travoprost.

DISCUSSION

Brinzolamide is a relatively new topical carbonic anhydrase inhibitor that has been shown to reduce IOP by 15–19% from baseline, given twice or three times daily, as monotherapy or added to timolol (10, 11). This reduction has been shown to be statistically equal to dorzolamide, the first topical carbonic anhydrase inhibitor available, but less than that of timolol (10-12). Brinzolamide also as been shown potentially additive to either latanoprost or travoprost in several smaller trials (13, 14).

The main advantage of brinzolamide over dorzolamide is the lack of ocular stinging. In regulatory trials brinzolamide was shown to sting less than dorzolamide based upon unsolicited adverse events and by a four-unit comfort grading scale (12). This finding was later confirmed by Stewart and associates using a visual analog scale at 10 seconds and 3 and 10 minutes following instillation (15). A significant difference in ocular pain was found at the 10-second post instillation time point with dorzolamide having the highest level (22.5±28.9) compared to brinzolamide (5.0±8.7) (15). The reason for this finding is not known exactly. It may be due to the inherent properties of the molecule itself or because brinzolamide has a neutral pH and dorzolamide is slightly acidic (12, 16).

The purpose of this study was to compare the efficacy and safety of timolol maleate compared to brinzolamide each given twice daily when added to travoprost given each evening in patients with open-angle glaucoma or ocular hypertension.

This study showed that both timolol maleate and brinzolamide when added to travoprost caused a reduction in IOP compared to baseline at 08:00, 12:00, and 16:00 hours as well as the diurnal curve. When the reduction in IOP was compared between medicines, as well as the absolute pressure levels at the individual time points and the diurnal curve, no statistical difference was found.

The extent of diurnal pressure reduction with brinzolamide added to travoprost in this study was slightly greater than observed in a prior trial which evaluated dorzolamide added to latanoprost (2.2 mmHg) (6). The reason for this difference between studies is not apparent by our results. However, the baseline pressures in the previous trial were several points lower, which may have slightly limited the ocular hypotensive response. Martinez de la Casa and associates have found approximately 30% reduction of brinzolamide and travoprost in 22 patients from untreated baseline (14). However, they did apparently evaluate the additivity of the topical carbonic anhydrase inhibitor specifically to travoprost (14).

The extent of diurnal pressure decrease in this current study with timolol added to travoprost was similar (3.2 mmHg) to several prior studies evaluating timolol added to latanoprost (2, 6, 8). In contrast, our results were slightly greater than that found by Pfeiffer and associates in the latanoprost/timolol regulatory trial (1.9 mmHg) (17). However, in our trial timolol was dosed twice daily and in the Pfeiffer study it was instilled only once per day as part of the fixed combination (17). Patients with known non-responsiveness to beta-blockers were not excluded from our trial. If these patients had been excluded it may have enhanced the average IOP reduction for the timolol group. By not excluding these patients our trial design is consistent with previous studies evaluating timolol and consis-

tent with the general population.

Our data are important for two reasons: first, timolol maleate, as a single agent, is classically believed to be more efficacious than a topical carbonic anhydrase inhibitor. Previous studies have noted, in direct comparisons, that timolol maleate monotherapy reduced the pressure more than topical carbonic anhydrase inhibitors (12, 18, 19). The reason why the IOP reductions between timolol and brinzolamide were similar in this trial as opposed to previous studies was not clear by our data. One explanation may be that because patients in this study were already treated with travoprost, they had lower baseline pressures than would be expected for untreated patients typically started on monotherapy. Consequently, because of the adjunctive use of the study medicines in this study, differences in their efficacy may have been less apparent clinically than when used as monotherapy.

Second, these data are important because timolol maleate, although an effective medication, may demonstrate systemic side effects. Although some of these adverse events are typically mild, including changes in mentation and aggravation of depression, others may be severe, including the worsening of active airway disease and cardiac block (20, 21). In contrast, brinzolamide has not been shown to have these systemic side effects (22). In addition, after more than 10 years of clinical experience, the topical carbonic anhydrase inhibitor class has demonstrated very few associated systemic side effects (23).

Consequently, the knowledge that topical carbonic anhydrase inhibitors can be used with equal efficacy to beta-blockers, when added to a prostaglandin analog, may help physicians treat glaucoma patients with more confidence when they do not want to prescribe a beta-blocker as second-line therapy.

Both timolol and brinzolamide, added to travoprost, were safe and generally well tolerated in this study. Ocular and systemic adverse events were relatively few. The most common was conjunctival hyperemia in 16% of brinzolamide and 6% of timolol treated patients. Conjunctival hyperemia is not a typical side effect from brinzolamide or timolol therapy and may have resulted from the prostaglandin analog therapy prescribed for both groups. A trend for less hyperemia was observed with the timolol group. However, any real difference in the incidence of hyperemia between groups should be confirmed with future trials. Importantly, a difference in conjunctival hyperemia rates was not observed between the travoprost/timolol fixed combination (14%) and travoprost alone (12%) in the Barnebey et al regulatory trial (24). Potentially, timolol could allow for less hyperemia because of its beta blockade effect, which might help prevent vessel dilation (25). Only 4.5% of patients (n=9) did not complete the protocol as designed. Only three of these discontinued patients were from adverse events, one on timolol and two on brinzolamide treatment.

This study showed that brinzolamide provides similar safety and efficacy compared to timolol maleate when added to travoprost.

This study did not evaluate other members of the topical carbonic anhydrase inhibitor or beta-blocker groups as study treatments or other prostaglandin analogs as the initial therapy. Results could have differed with other medications. Further research is needed to more fully understand the additive efficacy of topical carbonic anhydrase inhibitors and beta-blockers to prostaglandin analogs as well as the most safe and efficacious therapy for glaucoma patients to prevent progression.

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