A Randomized, Investigator-Masked, 4-Week Study Comparing Timolol Maleate 0.5%, Brinzolamide 1%, and Brimonidine Tartrate 0.2% as Adjunctive Therapies to Travoprost 0.004% in Adults with Primary Open-Angle Glaucoma or Ocular Hypertension

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ABSTRACT

Objective: The objective of this study was to assess the hypotensive efficacy of timolol maleate 0.5%, brinzolamide 1%, or brimonidine tartrate 0.2% ophthalmic solution, administered in conjunction with travoprost 0.004%, in patients with primary open-angle glaucoma (OAG) or ocular hypertension (OHT) whose intraocular pressure (IOP) did not meet the treatment target using travoprost 0.004% monotherapy.

Methods: This was a randomized, comparative, investigator-masked study. Patients with OAG or OHT treated with travoprost 0.004% monotherapy were randomized to receive 1 of the 3 adjunctive therapies (timolol maleate 0.5%, brinzolamide 1%, or brimonidine tartrate 0.2%), 1 drop BID in each randomized eye, in addition to 1 drop QD of travoprost for a period of 4 weeks. IOP was measured on days 0 (travoprost 0.004%) and 28 (travoprost 0.004% and adjunctive treatment). Adverse events were monitored on days 0 and 28 by patient interview.

Results: Twenty-nine patients with OAG (46 eyes) and 3 patients with OHT (6 eyes), with a total of 52 eligible eyes, completed the study; 28 eyes were from male patients and 24 were from female patients. In addition to continuing travoprost treatment, 20 eyes received timolol, 16 eyes received brinzolamide, and 16 eyes were treated with brimonidine. There were no significant differences among the groups in the mean (SD) IOP at baseline on day 0 (19.0 [4.1], 17.2 [3.5], and 17.0 [3.1] mm Hg, respectively; P = NS). On day 28, the reduction in mean (SD) IOP in eyes treated with brimonidine tartrate 0.2% was significantly smaller (2.3 [1.8] mm Hg vs 3.9 [1.8] mm Hg [P = 0.01]) and the mean (SD) percentage reduction in IOP was significantly smaller (13.4% [9.1%] vs 20.2% [7.5%] [P = 0.01]) when compared with timolol maleate 0.5%, and likewise when compared with brinzolamide 1% (4.0 [2.1] mm Hg [P = 0.02] and 22.7% [8.6%] [P = 0.006], respectively). The group treated with brinzolamide was associated with a similar reduction in IOP to timolol (P = NS for both mean [SD] IOP and percentage reduction in IOP compared with timolol monotherapy). Barring the occasional conjunctival hyperemia, which was excluded as an adverse event for the purposes of this study, no adverse events were recorded.

Conclusion: Brinzolamide 1% and timolol maleate 0.5% treatment were both associated with a significantly greater reduction in IOP compared with brimonidine 0.2% when administered as a nonfixed adjuvant to travoprost 0.004% in the treatment of patients with OAG and OHT whose IOP was inadequately controlled with travoprost monotherapy. All treatments were well tolerated. (*Clin Ther.* 2006;28:552–559)

Key words: open-angle glaucoma, humans, intraocular pressure, ophthalmic solutions, adverse events, therapeutic use, brinzolamide, timolol maleate, brimonidine tartrate, travoprost.

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INTRODUCTION

A positive correlation has been reported between the reduction of intraocular pressure (IOP) and a decrease in the incidence or stabilization of glaucoma.[1–4] Evidence of the absence, or retardation of loss, of visual field and even improvement in the sensitivity levels due to the reduction in IOP have also been reported.[5,6] Additionally, a reduction of IOP in patients with ocular hypertension (OHT) might be associated with a decrease in the risk of progressing to primary open-angle glaucoma (OAG).[7]

Therefore, treatments for glaucoma and OHT are geared toward the reduction of IOP to an individually determined level (ie, IOP target),[8] using medication, laser treatment, and/or surgery[9] to achieve this goal. The prostaglandin analogue travoprost ophthalmic solution* 0.004% has been reported to be highly effective and well tolerated in the treatment of OAG and OHT, has a once-daily administration regimen, and has a favorable adverse-event profile.[10,11]

Patients with advanced glaucoma and/or IOP might not reach treatment targets with monotherapy using prostaglandin or prostamide analogues, and might require supplementary treatment.[12,13] In these cases, if factors such as efficacy, tolerability, and compliance are taken into consideration when selecting an adjunctive treatment, the concomitant use of additional drugs would be an appropriate option for achieving target IOP.[14–17]

Robin et al[13] found that some patients undergoing treatment with prostaglandin and prostamide analogues required adjunctive treatment. In that study, 29.8% of patients treated with latanoprost 0.005% needed adjuvant ocular treatment. The same results were found in 24.3% of those treated with bimatoprost 0.03%.[13] Netland et al[18] found that adjunctive treatment was needed in only 8% of patients treated with travoprost 0.004%. In a study of the long-term effects of latanoprost 0.005% on IOP, Hedman and Alm[12] found that ~7% of patients required additional medication or needed to switch to another medication due to unsatisfactory control of IOP with monotherapy.

Timolol maleate is a nonselective β-adrenergic clocking agent that reduces IOP by decreasing aqueous secretion with little effect on episcleral venous pressures, facility of outflow or uveoscleral outflow.[19] Brinzolamide is a carbonic anhydrase inhibitor that reduces IOP by reducing secretions and, to a lesser extent, inducing acidosis.[20] Brimonidine tartrate is a relatively selective α_2-adrenergic agonist that reduces aqueous secretion production and increases uveoscleral outflow.[21]

Published studies comparing travoprost 0.004% with possible adjunctive therapies for glaucoma were not found in a literature search (a general search of MEDLINE using the key term *travoprost*). The purpose of this study was to assess the hypotensive efficacy and tolerability of timolol maleate 0.5%,† brinzolamide 1%,‡ and brimonidine tartrate 0.2%§ ophthalmic solutions BID, administered in conjunction with travoprost 0.004%, in patients with OAG or OHT whose IOP target was not reached during travoprost monotherapy.

SUBJECTS AND METHODS

This was a prospective, randomized, investigator-masked, comparative study conducted with parallel groups. The study was conducted in 2 medical centers in Brazil: the Ophthalmology Department at Federal University of Goiás in Goiânia and the Ophthalmologic Department of the Hospital Santa Casa de Misericórdia in São José do Rio Preto, São Paulo. The ethics committees of both institutions approved the study. Patients signed informed-consent forms to participate.

Patients with OAG or OHT, who had been treated with travoprost 0.004% monotherapy for ≥8 weeks and whose IOPs were unsatisfactory (ie, higher than the target pressure established by the examining doctor, based on the optic disc and visual field) took part in this study. The target pressure was based on individual criteria, and therefore, it was not standardized.

The criteria for inclusion of OAG were as follows: IOP baseline (without medication) or medical records indicating an IOP >21 mm Hg with or without medication on ≥2 occasions, gonioscopy examinations revealing wide angle,[22] 2 campimetric examinations using SITA Standard 24-2 (Humphrey Systems, Dublin, California), reliable readings as defined according to the criteria established by Anderson and Patella,[23] and optic disc with biomicroscopic alterations indicative of

*Trademark: Travatan® (Alcon Laboratories of Brazil, São Paulo, Brazil).

†Trademark: Glautimol® (Alcon Laboratories of Brazil).

‡Trademark: Azopt® (Alcon Laboratories of Brazil).

§Manufactured by Falcon Laboratories of Brazil, São Paulo, Brazil.

glaucoma (ie, overall narrowing or localized narrowing of the neural rim, typical vascular alterations, asymmetry of the optic cup >0.2 [cup-to-disc ratio] and hemorrhage).[24] The OHT subjects were included after ≥2 IOP measurements >21 mm Hg on 2 occasions, in the absence of any alterations indicative of glaucoma in the optic disc or the visual field (see criteria mentioned previously).

The exclusion criteria for both groups under study were as follows: refusal to take part in the study, desire to drop out of the study, inability to comply with the dosage, IOP >35 mm Hg, hypersensitivity to the active ingredients in the ophthalmic solution, any alteration in the biomicroscopic or fundoscopy examinations capable of changing the applanation tonometry (such as corneal scarring or keratoconus), a perimetric examination (such as macular degeneration) except in the case of glaucoma, recent history (6 months) of uveitis, herpes or ocular trauma, laser treatment or glaucoma surgery in the previous 3 months, vertical cup-to-disc ratio >0.8, threat of glaucoma in the area of fixation, need for surgery or doctor's advice of surgery, nephropathy or hepatopathy, history of or current cardiovascular or respiratory disease (such as chronic obstructive pulmonary disease, bronchial asthma, sinus bradycardia, 2nd and 3rd degree atrioventricular block, cardiogenic shock, cardiac failure, central or peripheral vascular disease, cardiac ischemia, orthostatic hypertension), depression, diabetes, hypoglycemia, thyroid disease, and myasthenia gravis. Patients who had been prescribed monoamine oxidase inhibitors or topical or systemic drugs that might alter the IOP (such as β-blockers or corticoids) were excluded. Also, women were excluded if they were pregnant or breastfeeding, or if they had a history of unreliable contraception.

During a 3-month screening period (April–June 2004), all patients who had received treatment with travoprost 0.004% for ≥8 weeks were examined for possible inclusion in the study. One investigator per institution conducted a review of the medical records and complete ophthalmologic examination of each patient (anamnesis, best corrected visual acuity, biomicroscopic examination of the anterior chamber, gonioscopy with a Posner 4-mirror lens, IOP measurement, and biomicroscopy of the fundus with a 78D lens and indirect fundoscopy, both in mydriasis). Automated perimetry was requested if it had not been performed in the previous 6 months or if the previous result was regarded as unreliable (due to fixation losses, false-negatives or false-positives). Both eyes of each patient were included in the study if they met the inclusion criteria.

One investigator was responsible for the randomization (done by lot) of the patient into one of the following groups: timolol maleate 0.5%, brinzolamide 1%, or brimonidine tartrate 0.2%. On day 0, or the first day of the study, the patient received an ophthalmic solution and was instructed to withhold from the investigators (except in situations related to tolerability and safety) the name of the eyedrops he or she was using, thereby eliminating any inclusion and examination bias. When both of the eyes of the same patient were included in the study, the randomization was conducted first in the right eye and then in the left eye. Patients were able to use different study drugs in different eyes.

All patients were instructed to keep their medication (travoprost 0.004% and adjunctive treatment) at room temperature and out of sunlight. The patient was instructed to instill 1 drop of the adjuvant medication in the inferior conjunctival sac, at 7 AM and 6 PM, while slightly closing the eyes and pressing the tear duct area for 2 minutes. One hour after nighttime administration of the adjuvant medication (ie, at 7 PM), 1 drop of travoprost 0.004% was to be administered, following the same instructions as those for instillation of the adjunctive treatment. All patients were interviewed to assess compliance ("Did you fail to use any of the drops anytime?" "If so, for how long?"). Failure to follow these instructions for >1 day during the course of the entire study period was regarded as sufficient cause to exclude patients from the study.

Patients were monitored by the same masked investigator at consultations conducted during the study (ie, on day 0 and day 28). IOP was measured using 1 tonometer located at each of the institutions. Measurements were always conducted at ~9 AM (Goldmann applanation tonometry[10,25,26]) and performed twice per eye. If there was a difference of >2 mm Hg between the first and second measurement, a third assessment was performed and the most discrepant value was discarded. The IOP recorded was the mean of the 2 readings. The efficacy between drugs was compared using the difference in IOP and the percentage of IOP decrease from baseline. Considering $P < 0.05$ as statistically significant, a difference of means of 1 mm Hg to be detected,

and the power of 80%, the estimated sample size for each group was 17.

During the study, any suspicion of an ocular or systemic event, regardless of its association to the treatment, was regarded as adverse. Due to the difficulty of establishing the cause of conjunctival hyperemia (which could result from using any of the ophthalmic solutions involved in the study),[9] it was excluded from the statistical analysis. Other adverse events were observed by the investigator or noted on the basis of patient complaints after the investigator had questioned them during each appointment. The patients were monitored individually until there was a satisfactory solution to the problem. If any adverse event (not observed) was considered serious or if the patient wished to discontinue the treatment, they were excluded from the study. However, compliance to methods was only determined through patient interviews.

The statistical analysis was conducted by means of SPSS software, version 11.5 (SPSS Inc., Chicago, Illinois). The normal sampling was obtained by means of the Kolmogorov-Smirnov test. Analysis of variance was used to assess the existence of hypotensive differences arising among the study groups (travoprost 0.004% with timolol 0.5%, brimonidine 0.2%, or brinzolamide 1%). With respect to hypotensive efficacy, the adjunctive ophthalmic solutions were compared in pairs by means of the Student *t* test for independent sample. Values of $P < 0.05$ were regarded as statistically significant. Considering the α error, the power of the test to detect differences was 84.2% in timolol comparisons and 78.1% in comparisons for brimonidine and brinzolamide.

RESULTS

During the screening, 35 patients were selected to take part in this study. Two patients refused to participate. On day 0, 33 patients received medication samples to be used in the study. Only 1 of the patients failed to return for the follow-up appointment. Twenty-nine patients (46 eyes) with OAG and 3 patients (6 eyes) with OHT finished the study for a total of 52 eyes; 28 were from male patients and 24 were from female patients.

In compliance with the randomization method, the 52 eyes were separated into 3 groups. Twenty eyes were treated with timolol maleate 0.5% (timolol group), 16 eyes with brinzolamide 1% (brinzolamide group), and 16 eyes with brimonidine tartrate 0.2% (brimonidine group). The mean (SD) age of the patients was 62.1 (10.1) years in the timolol group, 54.0 (12.0) years in the brinzolamide group, and 57.4 (10.0) years in the brimonidine group (P = NS).

There were no statistically significant differences found among the groups, in relation to the mean IOP at baseline (ie, day 0) while on travoprost 0.004% monotherapy (P = NS) (**Table**). In relation to hypotensive efficacy, differences in mean (SD) IOP values (P = 0.03) and in percentage change in IOP (P = 0.008) were observed (**Table**; **Figure**). When the IOPs were assessed between the pairs of ophthalmic solutions used (in addition to travoprost 0.004%), treatment with brimonidine tartrate 0.2% was associated with a significantly smaller reduction in mean (SD) hypertension results compared with timolol maleate 0.5% (2.3 [1.8] mm Hg vs 3.9 [1.8] mm Hg [P = 0.01]; 13.4% [9.1%] vs 20.2% [7.5%] [P = 0.01]) and brinzolamide 1% (4.0 [2.1] mm Hg [P = 0.02]; 22.7% [8.6%] [P = 0.006]). No significant differences were observed between timolol and brinzolamide (**Table**). No adverse events were reported by any of the study groups.

DISCUSSION

To determine which adjunctive drug, when used with travoprost 0.004%, would enable improved ocular hypotension performance, 3 out of 4 possible nonfixed associations were studied. Pilocarpine was not included in the study because its use is associated with several adverse events and it is an antagonist of travoprost 0.004%.[10,27] The 7 AM and 6 PM time points were chosen for the instillation of adjunctive treatment because the effect of β-blockers is reduced during sleep.[25,26] In addition, these time points were assumed to minimize the risk of cardiorespiratory adverse events because the heart rate is normally reduced during the night.[28,29] The 9 AM time point for measuring IOP was chosen because it coincided with the peak action of travoprost 0.004%[10] and the adjunctive therapies, given the instillation times.[9]

When used in association with travoprost 0.004%, all 3 adjunctive study groups had reductions in IOP at day 28. However, statistically significant differences were found when all groups were compared with each other. These differences might have been due to poorer ocular hypotensive performance recorded in the brimonidine group, both in terms of direct measure of mean (SD) IOP (P = 0.03) and in percentage of IOP reduction (P = 0.008). When comparing pairs of oph-

Table. Evaluation of ocular hypotension response among patients with primary open-angle glaucoma or ocular hypertension who were randomized to receive timolol maleate 0.5% (n = 20), brinzolamide 1% (n = 16), or brimonidine tartrate 0.2% (n = 16), in addition to travoprost 0.004%, for 28 days.

			P	
Variable	Mean (SD)	Range	ANOVA	Student *t* Test
Baseline IOP, mm Hg			0.1	
Timolol	19.0 (4.1)	14.0 to 26.0		0.1 vs brinzolamide or brimonidine
Brinzolamide	17.2 (3.5)	13.0 to 24.0		0.7 vs brimonidine
Brimonidine	17.0 (3.1)	14.0 to 23.0		
End-of-study IOP, mm Hg			0.1	
Timolol	15.1 (3.3)	11.0 to 22.0		0.08 vs brinzolamide, 0.5 vs brimonidine
Brinzolamide	13.2 (2.7)	10.0 to 19.0		0.1 vs brimonidine
Brimonidine	14.5 (2.5)	12.0 to 21.0		
Reduction in IOP, mm Hg			0.03	
Timolol	3.9 (1.8)	1.0 to 7.0		0.8 vs brinzolamide, 0.01 vs brimonidine
Brinzolamide	4.0 (2.1)	2.0 to 10.0		0.02 vs brimonidine
Brimonidine	2.3 (1.8)	–1.0 to 7.0		
% Change in IOP			0.008	
Timolol	20.2 (7.5)	5.5 to 36.9		0.3 vs brinzolamide, 0.01 vs brimonidine
Brinzolamide	22.7 (8.6)	12.5 to 47.6		0.006 vs brimonidine
Brimonidine	13.4 (9.1)	–7.1 to 35.0		

ANOVA = analysis of variance; IOP = intraocular pressure.

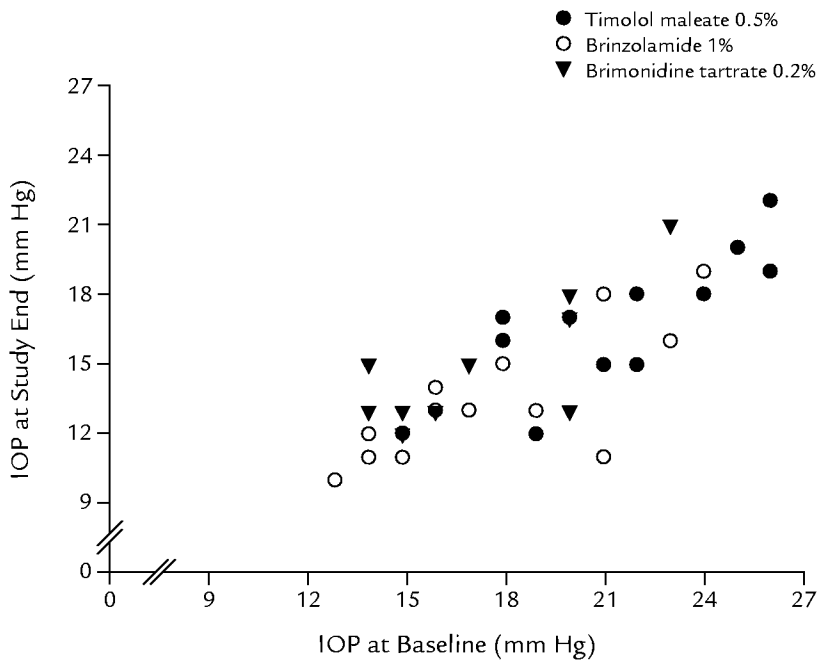

Figure. Distribution of intraocular pressure (IOP) before and after 28 days of nonfixed treatment with timolol maleate 0.5% (n = 20), brinzolamide 1% (n = 16), or brimonidine tartrate 0.2% (n = 16), in addition to continued travoprost 0.004% treatment, in patients with primary open-angle glaucoma or ocular hypertension.

thalmic solutions administered in conjunction with travoprost 0.004%, the brimonidine tartrate solution 0.2% was associated with smaller changes in IOP than timolol (both mean [SD] IOP and percentage change, $P = 0.01$) and brinzolamide (mean [SD] IOP, $P = 0.02$; percentage change, $P = 0.006$). The greatest statistically significant IOP reduction in mm Hg in the timolol group in relation to the brinzolamide group, when compared with brimonidine (0.01 vs 0.02), might be explained by the higher baseline mean (SD) IOP value in the first group in relation to the patients using brinzolamide (19.0 [4.0] mm Hg vs 17.2 [3.5] mm Hg). However, in this same comparison, we observed that the brinzolamide users were associated with a higher percent reduction in IOP, though it was not statistically significant. The reduction in IOP for the brinzolamide group was not significantly different from that of the timolol group.

In a study of the additive ocular hypotensive effect of prostaglandin analogue latanoprost 0.005%, O'Connor et al[30] concluded that the carbon anhydrase inhibitor dorzolamide 2% had a greater reduction in IOP (19.7%) when compared with β-blockers (12.3%) and brimonidine 0.2% (9.3%) ($P < 0.006$). However, despite some similarity to the results observed in our study, with the exception of the longer period of treatment (12 to 15 months) and the statistically significant difference between dorzolamide and β-blockers, the study by O'Connor et al had some major limitations. It was a retrospective, nonrandomized, nonblinded study; such a design has inherent problems. There are no references to the number of investigators or tonometers used or the time points for measuring IOP, which might cause considerable bias in the results, especially due to the absence of standardization of the time points for measuring IOP, influenced by the circadian rhythm.[25,26] Moreover, there were no descriptions of the types of β-blockers that were assessed in the study, which might affect the hypotensive strength of the drug under study.[31]

Regarding safety profile, it is important to note that any medication can cause side effects, due to individual reaction variations, which can be unpredictable in relation to the number and degree of severity of these effects.[32] With the introduction and topical use of carbon anhydrase inhibitors, the occurrence of adverse events has been reduced and practically limited to a burning sensation or blurred vision when instilled, thereby indicating that this class of drugs is well tolerated.[9,32] Changes in taste, drowsiness, or allergic reactions are associated with the use of α_2-adrenergic (~10%).[9,32] Studies have suggested that the incidence of ocular (usually a local and transient burning after instillation) or systemic adverse events with β-blockers is low (<5%).[28,29] However, special attention must be paid to the possibility of life-threatening adverse events (eg, heart and respiratory failure) in patients with cardiac arrhythmia, bradycardia, atrioventricular blockage, congestive heart failure, or bronchial asthma, especially among those patients who have undiagnosed heart or lung problems.[28,29,32] Additionally, tachyphylaxis to β-blockers has been observed, whereby their action is diminished over the period of treatment, which is a crucial factor in a chronic disease such as glaucoma.[30]

No systemic adverse events were reported by the patients or observed by the investigators in this study on days 0 or 28. The only adverse reaction observed in the study groups was a slight occasional conjunctival hyperemia; however, hyperemia was not recorded as an adverse event because all study drugs might result in hyperemia. This was a limitation of the study. All 3 study drugs were well tolerated by the participants.

The limitations of this study include the small patient sample (and relatively few eyes), short duration, single-masked design, and exclusion of hyperemia as a side effect. Additionally, randomization of different eyes in the same patient to 2 different adjunctive medications excludes independency of the IOP-lowering effect between the 2 eyes, since crossover effect might be possible. This is the major limitation of the study. However, it is the first prospective, randomized, investigator-masked study to assess the additive effects of brinzolamide 1%, timolol maleate 0.5%, and brimonidine 0.2% when administered in conjunction with travoprost 0.004% to patients with OAG or OHT.

CONCLUSIONS

These results suggest that brinzolamide 1% and timolol maleate 0.5% were more effective than brimonidine 0.2%, when administered as nonfixed adjunctive treatment with travoprost 0.004%, in the treatment of patients with OAG or OHT whose IOP was not adequately controlled with travoprost monotherapy. However, there were no significant differences between timolol maleate 0.5% and brinzolamide 1%. All treatments were well tolerated.

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