Comparison of the Ocular Hypotensive Efficacy of Adjunctive Brimonidine 0.15% or Brinzolamide 1% in Combination with Travoprost 0.004%

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Purpose: To compare efficacies of adjunctive therapy with brimonidine 0.15% and adjunctive therapy with brinzolamide 1% in combination with travoprost 0.004%.

Design: Three-month randomized, parallel-group, double-masked, multicenter clinical trial.

Participants: Patients with primary open-angle glaucoma, exfoliation glaucoma, or ocular hypertension with intraocular pressure (IOP) > 18 mmHg on monotherapy with travoprost (N = 163).

Methods: Patients were randomized to receive adjunctive therapy with twice-daily brimonidine (N = 79) or twice-daily brinzolamide (N = 84). Treatment efficacy was assessed after 1 and 3 months of combination therapy. Intraocular pressure was measured at 8 AM, noon, and 4 PM at baseline (on travoprost monotherapy) and after 3 months of combination therapy. Mean diurnal IOP was defined as the average of the IOP measurements at these 3 time points. Adverse events were recorded at each visit.

Main Outcome Measure: Difference between treatment groups in mean diurnal IOP at month 3, adjusted for difference in baseline IOP, using analysis of covariance.

Results: Mean diurnal IOPs (± standard error of the mean) at baseline were 21.7±0.33 mmHg in the brimonidine group and 21.1±0.29 mmHg in the brinzolamide group ($P = 0.16$). Mean diurnal IOPs at month 3 were 19.6±0.41 mmHg in the brimonidine group and 18.4±0.33 mm Hg in the brinzolamide group ($P = 0.019$). At month 3, mean diurnal IOPs, adjusted for difference in baseline IOP, were 19.3±0.27 in the brimonidine group and 18.6±0.25 in the brinzolamide group ($P = 0.035$).

Conclusions: The combination of travoprost and brinzolamide was statistically significantly more efficacious than the combination of travoprost and brimonidine in lowering IOP. The clinical significance of this difference is uncertain. *Ophthalmology 2007;114:1248–1254 © 2007 by the American Academy of Ophthalmology.*

Some eyes treated with a prostaglandin analog do not achieve adequate intraocular pressure (IOP) reduction, and a second agent may be required. Both the Ocular Hypertension Treatment Study and Collaborative Initial Glaucoma Treatment Study have shown that many patients require multiple medications to meet target pressures.[1,2] In the Ocular Hypertension Treatment Study, for example, the overall proportion of patients requiring a multiple medication regimen was approximately 40%.[1] This demonstrates the importance of additive medical therapy in the management of glaucoma, even with the advent of the newer, more effective agents. Multiple medications are also more commonly necessary to achieve the low pressures proven to minimize the risk of progressive visual field (VF) loss.[2–4]

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However, there are scant data in the literature to guide the selection of a specific adjunctive agent in an eye already on a prostaglandin analog.

Two medication classes commonly used as adjunctive therapy to prostaglandin analogs are topical carbonic anhydrase inhibitors (CAIs) and topical α-agonists. Previous, mostly noncomparative studies have demonstrated the additive ocular hypotensive efficacy of the topical CAIs brinzolamide 1% ophthalmic suspension (Azopt, Alcon Laboratories, Fort Worth, TX)[5] and dorzolamide 2% (Trusopt, Merck & Co., Inc., Blue Bell, PA)[6,7] and the topical α_2-adrenergic agonist brimonidine 0.2% (Alphagan, Allergan, Inc., Irvine, CA)[8,9] as adjunctive treatment to monotherapy with a prostaglandin analog. There is a paucity of prospective data comparing IOP-lowering efficacies of CAIs and α-agonists in eyes already on a prostaglandin analog. This prospective, multicenter, double-masked clinical trial was designed to evaluate the IOP-lowering efficacy of twice-daily brimonidine 0.15% purite (Alphagan-P 0.15%, Allergan) versus twice-daily brinzolamide 1% ophthalmic suspension as adjunctive therapy to travoprost 0.004% (Travatan, Alcon Laboratories) in eyes with glaucoma or ocular hypertension.

Patients and Methods

Study Design Summary

The protocol was approved by the appropriate institutional review boards for each center and followed the tenets of the Declaration of Helsinki. Informed consent was obtained from each patient before study enrollment. The study was posted on the clinicaltrials.gov Web site.

This 3-month randomized, parallel-group, double-masked study was conducted at 18 centers in the United States representing both academic and private practices. After a screening visit, patients began travoprost 0.004% monotherapy administered once daily at 8 PM. All other medications were discontinued during this time. After 1 month, eyes with IOP > 18 mmHg were randomly assigned to adjunctive therapy with either brimonidine 0.15% or brinzolamide 1% at 8 AM and 8:05 PM. Study participants returned 1 and 3 months later for follow-up examinations.

Patient Selection

Table 1 details the inclusion and exclusion criteria.

Table 1. Inclusion and Exclusion Criteria

Inclusion
Age ≥ 35 yrs
Unilateral or bilateral primary open-angle glaucoma, ocular hypertension, or pseudoexfoliation syndrome
An insufficient response to monotherapy, defined as mean diurnal IOP > 18 mmHg on travoprost at baseline
Exclusion
Closed, occluded, or potentially occludable anterior chamber angle
Mean diurnal IOP > 32 mmHg on travoprost
History of angle closure
Previous intraocular surgery, except uncomplicated clear cornea phacoemulsification, or laser trabeculoplasty
Laser trabeculoplasty or phacoemulsification within 3 mos before the screening visit
Central corneal thickness < 500 μm or > 600 μm as measured by ultrasonic pachymetry
Ocular or periocular inflammation within 3 mos before screening (except related to mild blepharitis or seasonal allergic conjunctivitis)
History of uveitis or previous intraocular inflammation (other than postoperatively)
Hypersensitivity or intolerance to sulfonamides, α-agonists, prostaglandin analogs, or benzalkonium chloride
Use of any corticosteroids for over 1 wk within 3 mos of screening or likely need for any corticosteroids during the study (except inhaled, nasal, or topical nonocular)
Use of systemic medications known to affect IOP (e.g., α-agonists, β-antagonists, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers), unless in use for ≥3 mos at a stable dose and expected to be continued at the same dose for the duration of the study
Use of any investigational medication within 1 mo before baseline visit
Female-specific
Pregnancy
Women of childbearing potential not using effective contraception

IOP = intraocular pressure.

Study Visits

To ensure that inclusion criteria were fully met, an initial screening visit was conducted at least 4 weeks before the baseline visit. At that time, a medical and ophthalmic history was obtained. Blood pressure, heart rate, and best-corrected visual acuity (VA) using Early Treatment Diabetic Retinopathy Study/Bailey–Lovie VA charts were measured. Goldmann applanation tonometry, ophthalmoscopy, external examination, slit-lamp biomicroscopy, and gonioscopy were performed. Central corneal thickness was measured by ultrasonic pachymetry 3 times for each eye. Thicker measurements could indicate that the pachymetry probe may not have been perpendicular to the cornea. Therefore, the lowest of the 3 measurements was considered most accurate and was used to determine eligibility.

Concomitant medications were recorded, and all ocular hypotensive therapy was discontinued simultaneous with the initiation of at least 4 weeks of travoprost 0.004% monotherapy. This was followed by a baseline evaluation. If eligible, subjects were given a randomly assigned adjunctive drug and reassessed at 1 and 3 months. The study headquarters randomized eligible patients on a block basis, stratified by center, to assure similar numbers in each drug treatment group and to prevent site-specific biases.

Brinzolamide and brimonidine were rebottled, masked, and labeled, with the codes retained by study management personnel at the study headquarters who had no patient contact. The intent was double masking by rebottling in generic containers without identifying labels and coding the adjunctive medications to conceal drug identity from those with patient contact. Hence, the study was double masked. However, given that the drops appear dissimilar, masking of some of the study subjects may not have been achievable because some subjects may have previously used either of the randomized study medications and could have been familiar with their appearance.

Data collected and procedures performed at each visit are summarized in Table 2 (available at http://aaojournal.org).

Adverse events (AEs) were recorded and graded at the month 1 and month 3 study visits as well as at any unscheduled visits. The investigator determined whether the AE was or was not related to study medications. Every AE was referred to the Data Safety and Monitoring Committee.

All IOP measurements were performed by an examiner and separate reader before dilation. The same examiner performed all IOP measurements on a given patient throughout the study. A

single calibration-checked Goldmann applanation tonometer was used for a given subject throughout the study. Two IOP measurements were obtained for each eye, alternating right to left, starting with the right eye, and if the difference between measurements exceeded 2 mmHg in the same eye, a third IOP measurement was performed for that eye. The mean of the 2 or 3 measurements obtained was used for analysis.

Intraocular pressure at the screening visit and unscheduled visits was determined at any time of the day. Month 1 IOP was measured only at 4 PM. Baseline and month 3 IOPs were measured at 8 AM, noon, and 4 PM ± 30 minutes. The mean diurnal IOP at the baseline and month 3 visits was defined as the mean of the IOP measurements at 8 AM, noon, and 4 PM. The difference in mean diurnal IOP, adjusted for difference in baseline IOP, between the 2 treatment groups at month 3 was the primary outcome measure. Secondary outcome measures included IOP at 8 AM, noon, and 4 PM at month 3 and change in IOP from baseline for each time point at month 3.

Treatment Schedule

Patients requiring bilateral therapy were treated identically in both eyes. Only those eyes meeting inclusion criteria were analyzed. A fellow eye not meeting all inclusion criteria but having none of the exclusion criteria also was treated with the study drug in the same manner as the study eye. No other ocular hypotensive therapy was permitted. All subjects received travoprost at 8 PM each day and the adjunctive medication at 8 AM and 8:05 PM. A window of 1 hour on either side of the designated times was acceptable. Study medication was administered after the 8 AM IOP determination on the month 3 study visit. For each visit, subjects reported when the last drops were administered and that time was recorded.

Variables and Analyses

The mean of the IOP measurements obtained for each patient and time point was used for analysis. The IOP of the study eye was used to represent the IOP of the patient if only one eye qualified for the study. If both eyes of a subject were designated study eyes, the mean of IOP recordings from both eyes at each measurement time was used for analysis. The unit of measurement throughout was the patient. This commonly used method reduces within-patient variability.[10]

Because the IOP measurements at month 3 were expected to be highly correlated with the baseline mean diurnal IOP, the primary efficacy variable was the mean diurnal IOP at month 3 adjusted for each subject's baseline mean diurnal IOP using analysis of covariance (ANCOVA). Secondary end points included unadjusted mean IOP difference, change in IOP from baseline to month 3 for each time point (8 AM, noon, and 4 PM), and change in mean diurnal IOP. In addition, 2 post hoc responder analyses were performed to determine the proportion of subjects in each group reaching a threshold level of 15% IOP reduction and reaching a 2-mmHg IOP reduction. No other post hoc analyses or threshold values were investigated.

Intent-to-treat (ITT) efficacy analyses included all patients who received study medication at baseline and who had valid month 3 IOP data. If a patient missed any of the 3 time points, the mean diurnal IOP for that eye was considered missing data. Because IOP was not constant throughout the day, the elimination of a time point could bias the mean diurnal IOP. Per-protocol analyses, which excluded patients who had major protocol violations, were conducted to confirm ITT results.

Safety analyses included all randomized patients and both study and treated fellow eyes. Adverse events were coded. The frequency and severity of ocular and systemic AEs and numbers of patients affected were summarized by treatment group, and confirmed whether the AE was related to the study drugs. For the purposes of AE reporting, travoprost was considered a study drug, and therefore, AEs could occur anytime after screening.

The significance of differences between groups in primary and secondary outcome variables was analyzed using ANCOVA. The initial model included treatment group and center as factors and baseline mean diurnal IOP and interaction between treatment and baseline mean diurnal IOP as covariates. Center was not a significant variable and was removed from the model. When the interaction between treatment and baseline mean diurnal IOP was not significant, it was not included in the final analysis. Ninety-five percent confidence intervals were calculated for each treatment group using the final model including the interaction term, if significant. In addition, 2-sample *t* tests were used to evaluate differences between treatments without adjusting for covariates.

Time-from-treatment analysis was performed using regression analysis with repeated measures. Data were rearranged sequentially: 4 hours (noon), 8 hours (4 PM), and 12 hours (8 AM) from when the study drugs were last dosed. Outcome variables include IOP at month 3 and change of IOP from baseline to month 3. The independent variables were treatment group and time from last eyedrop as well as the interaction between the 2 main effects.

Between-treatment group differences in other continuous variables were evaluated using 2-sample *t* tests. The Fisher exact test was used to evaluate the significance of differences between groups in categorical variables. The effects of eye color and race on IOP by drug were analyzed by a 2-way analysis of variance (ANOVA). All statistical tests were 2 tailed, and the significance level (α) was 0.05. Statistical analyses were conducted using SAS 9.1 (SAS Institute, Cary, NC).

Sample size was based upon detecting a difference between the 2 treatment groups of 1.5 mmHg in mean diurnal IOP at month 3, with a significance level of 0.05 and power of 0.80. To estimate the sample size, a conservative standard deviation (SD) was used. Historical data from other drug therapy studies showed the SD ranging up to 4.0 mmHg.[11] The sample size per treatment group was estimated to be 64, 86, or 112 if the SD was 3, 3.5, or 4 mmHg, respectively. Thus, the study planned to recruit 112 subjects per group. To reevaluate the validity of the initial SD estimate, a masked computation of the SD of IOP was planned after 60 patients completed the study.

Results

Two hundred twenty-seven patients from 18 sites were screened, with study centers contributing from 3 patients to 27 patients. Based on the masked analysis, the revised SD was 3 mmHg. Thus, the sample size requirement was revised downward to 70 per group, allowing for 10% overenrollment for dropouts. Due to rapid screening with fewer screen failures toward the end of recruitment, 163 (72%) subjects were randomized: 79 (48.5%) to the brimonidine group and 84 (51. 5%) to the brinzolamide group over 17 months between February 2004 and June 2005. The ITT analyses included all randomized individuals.

Subject demographics are shown in Table 3. There were no significant differences between groups for any variable. Proportions of patients with 2 study eyes were similar in the 2 treatment groups (brimonidine, 64/79 [81%]; brinzolamide, 68/84 [81%]). Study diagnosis was considered as mixed when one eye carried one eligible diagnosis and the other eye carried another.

Ten patients withdrew for reasons summarized in Table 4 (available at http://aaojournal.org). Nine patients (6 on brimonidine and 3 on brinzolamide) left the study because of AEs. One patient failed to return for the 3-month follow-up visit. The

Table 3. Demographic Characteristics at Baseline

Characteristic	Brimonidine (N = 79)	Brinzolamide (N = 84)	P Value
Age (yrs) [mean ± SD (range)]	62.91±9.34 (41–79)	64.00±10.25 (39–83)	0.478
Gender			0.638
Male	35 (44.3%)	34 (40.5%)	
Female	44 (55.7%)	50 (59.5%)	
Race			0.437
Caucasian	41 (51.9%)	51 (60.7%)	
African American	29 (36.7%)	27 (32.1%)	
Hispanic	7 (8.9%)	6 (7.2%)	
Other	2 (2.5%)	0 (0.0%)	
Study eye(s)			0.654
Both	64 (81.0%)	68 (81.0%)	
Right only	9 (11.4%)	12 (14.3%)	
Left only	6 (7.6%)	4 (4.8%)	
Diagnosis of study eye			0.215
Primary open-angle glaucoma	49 (62.0%)	60 (71.4%)	
Ocular hypertension	26 (32.9%)	22 (26.2%)	
Pseudoexfoliation syndrome	0 (0.0%)	1 (1.2%)	
Mixed	4 (5.1%)	1 (1.2%)	

SD = standard deviation.

cohort was composed of the remaining 72 (72/79) brimonidine subjects and 81 (81/84) brinzolamide subjects who returned for the 3-month visit. However, 1 patient in the brinzolamide group contributed only a single IOP at 8 AM at the month 3 visit.

The drug-related AEs reported throughout the study are listed in Table 4. The most frequently occurring AEs were allergy, eye pain, headache, hyperemia, and taste disturbance. However, the incidences of AEs did not significantly differ between groups.

There were 2 patients who were enrolled but did not meet the inclusion/exclusion criteria. The ITT analyses also included a subject who had been randomized to receive brimonidine but was initially given brinzolamide for 5 days until the error was noted and corrected.

Mean diurnal IOPs (± standard error of the mean [SEM]) in the 2 treatment groups were similar at baseline (brimonidine, 21.7±0.33 mmHg; brinzolamide, 21.1±0.29 mmHg; $P = 0.16$.). Table 5 summarizes unadjusted mean IOP by treatment group and time point at baseline and month 3. The *P* values were obtained by a 2-sample *t* test.

At month 3, comparison between treatment groups resulted in an unadjusted mean IOP significantly lower in the brinzolamide group than in the brimonidine group at 8 AM ($P = 0.007$) and at 4 PM ($P = 0.007$). The mean diurnal IOP was lower in the brinzolamide group as well ($P = 0.019$). Unadjusted mean IOPs measured at noon were similar in the 2 groups at month 3 ($P = 0.292$).

The correlations between baseline and month 3 IOP measurements were explored for mean diurnal, 8 AM, noon, and 4 PM and were found to be 0.73, 0.69, 0.63, and 0.64, respectively (Pearson correlation coefficient). These high correlations indicate that an adjustment of the baseline mean diurnal IOP is needed for comparison of IOP at month 3 between groups. Thus, ANCOVA was performed to compare month 3 IOP with adjustment for baseline mean diurnal IOP. The results from the ANCOVA differ from the previous unadjusted 2-sample *t* test findings. Analysis of covariance showed a statistically significant difference of 0.7 mmHg favoring brinzolamide ($P = 0.035$) (Table 6).

After adjustment, the main effect of treatment in IOP reduction from baseline to month 3 at 8 AM was not significant ($P = 0.077$; Table 6); however, month 3 IOP reduction at 8 AM depends on the baseline IOP (Fig 1), which showed a significant interaction ($P = 0.031$; the 2 regression lines were not parallel). Intraocular pressure at 8 AM in the brimonidine group was reduced by 1.8 mmHg regardless of baseline mean diurnal IOP, but with brinzolamide, an IOP reduction of approximately 0.26 mmHg was observed for each 1-mmHg increase in baseline IOP, a significant interaction effect.

Time-from-treatment analysis using regression with repeated measures was performed on reordered data depicting 4 hours

Table 5. Unadjusted Mean Intraocular Pressure (± Standard Error of the Mean) at Baseline and Month 3

	Baseline			Month 3		
	Brimonidine (N =79)	*Brinzolamide (N = 84)*	P *Value*	*Brimonidine (N = 72)*	*Brinzolamide (N = 80)*	P *Value*
8 AM	22.6±0.37	22.2±0.34	0.343	20.9±0.48	19.2±0.38*	0.007
Noon	21.6±0.38	20.8±0.31	0.083	18.7±0.45	18.1±0.38	0.292
4 PM	20.9±0.37	20.4±0.33	0.278	19.2±0.40	17.7±0.37	0.007
Diurnal	21.7±0.33	21.1±0.29	0.160	19.6±0.41	18.4±0.33	0.019

*N = 81 patients.

Table 6. Adjusted Mean Intraocular Pressure (IOP) and IOP Change from Baseline to Month 3 (± Standard Error of the Mean) and 95% Confidence Interval at Baseline Mean IOP of 21.42 mmHg

	IOP at Month 3			IOP Change from Baseline to Month 3		
Time	*Brimonidine (N = 72)*	*Brinzolamide (N = 80)*	P *Value*	*Brimonidine (N = 72)*	*Brinzolamide (N = 80)*	P *Value*
8 AM	20.6±0.33 (20.0–21.3)	19.5±0.31* (18.9–20.1)	0.011	−1.8±0.32 (−2.4 to −1.2)	−3.0±0.30* (−3.6 to −2.4)	†
Noon	18.5±0.34 (17.8–19.2)	18.3±0.32 (17.7–19.0)	0.709	−2.8±0.37 (−3.6 to −2.1)	−2.8±0.35 (−3.5 to −2.1)	0.922
4 PM	18.9±0.31 (18.3–19.5)	17.9±0.29 (17.3–18.4)	0.012	−1.7±0.32 (−2.3 to −1.0)	−2.8±0.31 (−3.4 to −2.2)	0.010
Diurnal	19.3±0.27 (18.8–19.9)	18.6±0.25 (18.1–19.1)	0.035	−2.1±0.27 (−2.6 to −1.6)	−2.8±0.25 (−3.3 to −2.4)	0.035

*N = 81.
†The interaction between treatment and baseline mean diurnal IOP from analysis of covariance was significant ($P = 0.031$), as evidenced by a negative slope (greater change from baseline) for brinzolamide versus the constant horizontal line for brimonidine in Figure 1. Significant interactions were not observed for any other time point.

(noon), 8 hours (4 PM), and 12 hours (8 AM) after last dosing of randomized study drugs (Fig 2). Outcome variables include IOP at month 3. The interaction between the 2 main effects, treatment group and time from last eyedrop, was significant ($P = 0.03$). The linear trend over time from when medication was last dosed differed significantly by drug over time, with more sustained IOP lowering with brinzolamide.

Intraocular pressures at the month 1 visit did not differ between the treatment groups ($P = 0.53$) using a 2-sample t test. Mean IOPs (± SEM) were 18.62±0.38 for brimonidine and 18.30±0.31 for brinzolamide. The 4 PM IOP at the month 3 visit was statistically significantly lower than at the month 1 visit by 0.77 mmHg ($P = 0.01$) in the brinzolamide group. There was no corresponding significant change in IOP between the month 1 and month 3 visits in the brimonidine group.

Intraocular pressure reductions in patients of African ancestry were compared with those in Caucasians by study drug using a 2-way ANOVA. Mean diurnal IOP at month 3, IOP at the 3 time points at month 3 (8 AM, noon, and 4 PM), and change in IOP from baseline were analyzed. Ethnicity was not significant.

The percentage (frequency) of patients in each group reaching a threshold level of 15% or 2-mmHg IOP reduction at month 3 is shown in Table 7. Percentages of patients reaching 15% IOP reduction at all 3 time points were 6.95% for brimonidine and 20% for brinzolamide. Although the percentages were low in both groups, the difference between groups was statistically significant ($P = 0.033$). Similarly, percentages of patients reaching the 2-mmHg IOP reduction threshold at all 3 time points were 22.22% for brimonidine and 43.25% for brinzolamide ($P = 0.006$).

After excluding 3 subjects who had protocol violations, a per protocol analysis was performed, and no statistically significant differences were found compared with the ITT analysis.

Discussion

After adjustment for baseline IOP, the 3-month IOP differences were statistically significant, for the 8 AM, 4 PM, and mean diurnal measurements (1.1, 1.0, and 0.7 mmHg, respectively) favoring brinzolamide. The clinical significance of these findings is unclear because the mean differences between groups are small. However, in some individual

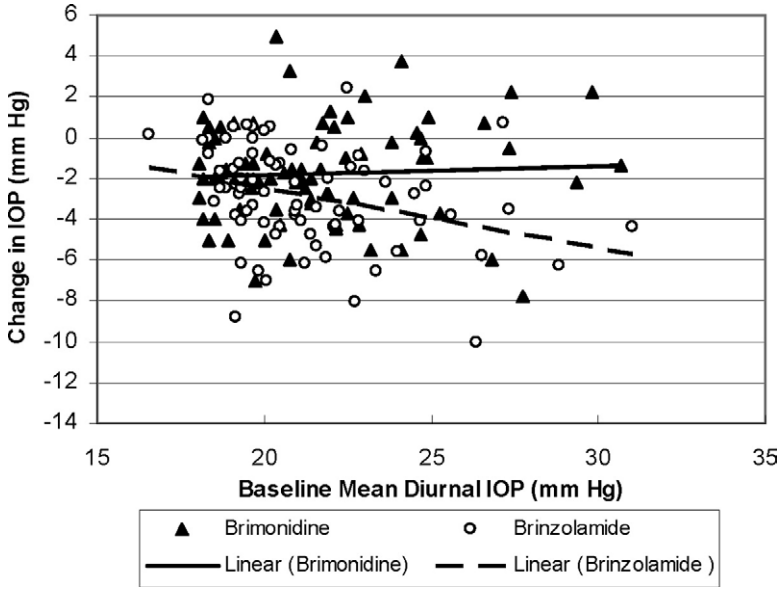

Figure 1. Mean diurnal intraocular pressure (IOP) at baseline versus IOP change from baseline at month 3 at 8 AM. The analysis of covariance interaction between treatment groups and baseline mean diurnal IOP was significant ($P = 0.031$), as evidenced by a negative slope (greater change from baseline) for brinzolamide versus the constant horizontal line for brimonidine.

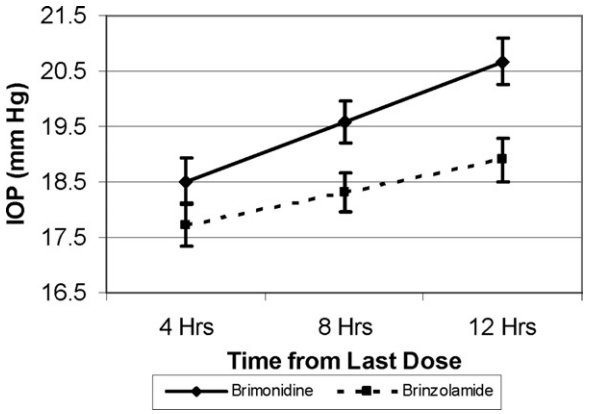

Figure 2. Intraocular pressure (IOP) (estimated mean from regression analysis ± standard error of the mean) as a function of time from last dose of adjunctive medication.

patients the differences are larger, as demonstrated in the responder analysis.

There was a smaller magnitude of IOP reduction with brimonidine at 8 AM and 4 PM (12 and 8 hours after administration of adjunctive therapy, respectively). However, at the noon time point (4 hours after administration of adjunctive therapy) there was no significant difference in magnitude of pressure reduction between the 2 agents. Furthermore, there was a more consistent IOP lowering throughout the day, ranging from 2.7 to 3.0 mmHg in the brinzolamide group and from 1.7 to 2.9 mmHg in the brimonidine group. Consistent IOP lowering may be important in preventing progression of glaucoma.[12,13]

Previous studies comparing the efficacy of the 3 most widely used prostaglandin analogs—bimatoprost, latanoprost, and travoprost—have been reported.[14,15] However, a PubMed search did not reveal direct comparative studies examining possible differences between prostaglandin analogs when used in combination with other agents. Similarly, little information was found comparing brinzolamide and dorzolamide as adjunctive therapy to prostaglandin analogs. The only study identified suggested that additions of brinzolamide and dorzolamide are equivalent when administered to patients already on a combination of latanoprost and a β-blocker.[16] Although findings in the current study may be clinically applicable to the various combinations of different prostaglandin analogs and topical CAIs and even to the various concentrations of brimonidine, there may be differences in additive efficacy and safety not yet elucidated.

There are few data comparing the effects of adding topical CAIs or topical α-agonists to prostaglandin analogs. In one retrospective study, dorzolamide was found to be more effective in lowering IOP than timolol or brimonidine 0.2% as adjunctive therapy in eyes already on latanoprost.[17] Additionally, Konstas et al reported in a double-masked crossover trial that there was no difference between adjunctive dorzolamide twice daily and brimonidine 0.15% twice daily in combination with latanoprost in 24-hour IOP measurements after 6 weeks of adjunctive therapy.[18] In that study, the additive effects of brimonidine after monitored drug administration at the same time points as in the current study for after drop administration were 3.4 mmHg after 4 hours, 2.1 mmHg after 8 hours, and 2.0 mm after 12 hours. These results are similar to those in the current study. However, additive effects of dorzolamide were 2.6, 2.4, and 2.5 mmHg at 4, 8, and 12 hours after administration, respectively, slightly less than when brinzolamide was added to travoprost in the current investigation. It is possible that differences in the results of these 2 studies are due to methodological considerations, including sample size and populations and duration of treatment (1 month in Konstas et al vs. 3 months in the current study). The present report is the third to detect additional IOP lowering with a topical CAI after 3 months of therapy versus 1 month. The study by Konstas et al looked at only IOP after 6 weeks of dorzolamide therapy.[18] Another possibility is that the combination of a prostaglandin analog and brinzolamide differs from the combination with dorzolamide or that the CAIs add to the various prostaglandins differently. More recently, Reis et al,[19] in a 4-week study, compared timolol 0.5%, brinzolamide 1%, and brimonidine 0.2% twice daily in addition to travoprost. In that small, randomized, observer-masked trial, no difference was found between timolol and brinzolamide, but both agents lowered pressure significantly more than brimoninidine. The results of the current study are consistent with those findings.[19]

To facilitate comparisons, this study duplicated most of the methodologies used in previously published adjunctive therapy trials of this type.[11] The selection of subjects with an insufficient response to monotherapy defined as IOP > 18 mmHg was based on the findings of the Advanced Glaucoma Intervention Study, which reported that among subjects with IOP < 18 mmHg at all visits, VFs, on average, remained stable.[3] The noon time point was chosen as peak effect rather than 10 AM to spread the evaluations equally into 4-hour increments after last-dose administration. In a prospective crossover trial examining the differences be-

Table 7. Percent (Frequency) of Patients Reaching the Reduction Criteria

IOP at Month 3	Brimonidine (N = 72)	Brinzolamide (N = 80)	*P* Value
≥15% reduction from baseline			
8 AM	25.0 (18)	39.5 (32)*	0.060
Noon	43.1 (31)	43.8 (35)	1.000
4 PM	29.2 (21)	45.0 (36)	0.047†
Diurnal	27.8 (20)	40.0 (32)	0.126
At all 3 time points	6.9 (5)	20.0 (16)	0.033†
≥2-mmHg reduction from baseline			
8 AM	51.4 (37)	66.7 (54)*	0.070
Noon	58.3 (42)	62.5 (50)	0.622
4 PM	47.2 (34)	66.3 (53)	0.022†
Diurnal	50.0 (36)	61.3 (49)	0.192
At all 3 time points	22.2 (16)	43.3 (35)	0.006†

IOP = intraocular pressure.
*N = 81.
†Significantly different in distributions.

tween brimonidine and dorzolamide used twice daily as monotherapy, the only diurnal time point at which there was a significant difference was 2 hours after administration, with IOP being lower in the brimonidine treated group.[20] The present study did not evaluate the 2-hour-after-dosage time point, and it is possible that brimonidine may lower IOP more at this time point than brinzolamide.

It was felt that excluding unusually thick or thin corneas would avoid error in IOP measurement due to artifact. The thinner corneas were excluded because the relationship between IOP and central corneal thickness may not be linear and may account for greater measurement errors as readings divert from normal. The effects of central corneal thickness on drug absorption into the eye are unknown as well.

In a post hoc analysis, we investigated the proportion of subjects in whom an additional 15% reduction in IOP was achieved with the adjunctive agent and also in whom an additional 2-mmHg IOP reduction was achieved. These thresholds were the only ones analyzed, and they were selected because (1) the American Academy of Ophthalmology preferred practice guidelines[21] recommend that in patients on therapy for glaucoma in whom progression occurs, an additional 15% reduction in IOP should be achieved and (2) 2 mm seems a reasonable minimum reduction for balancing the risks, costs, and benefits of additional therapy. The results of both of these analyses showed a low response rate and suggest that neither therapy should be considered the ideal agent to add to a prostaglandin analog. New or different classes of medications need to be developed for combination therapy.

In conclusion, this study demonstrates a small but statistically greater IOP-lowering efficacy of brinzolamide 1% compared with brimonidine 0.15% when used adjunctively with the prostaglandin analog travoprost after 3 months of therapy. Although the clinical significance of these small differences is uncertain, the efficacy and consistency in IOP reduction should be considered when deciding which medication to add for patients with glaucoma or ocular hypertension insufficiently controlled on a prostaglandin analog.

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Appendix: Additivity Study Group

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Table 2. Schedule of Procedures at Study Visits

Scheduled Visits	Screening	Baseline	Month 1	Month 3	Unscheduled
Time	Any	8 AM, noon, 4 PM	4 PM	8 AM, noon, 4 PM	Any
Review inclusion/exclusion criteria	X	X			
Obtain written informed consent	X				
Pregnancy test	X				
Medical history	X				
Concomitant medications	X	X	X	X	
Blood pressure/pulse	X	X	X	X	
Ocular history and medication	X				
Randomization		X			
Visual acuity	X	X	X	X	
Slit-lamp biomicroscopy	X	X	X	X	
Intraocular pressure	X	X	X	X	
Gonioscopy	X				
Indirect ophthalmoscopy	X				
Optic disc examination	X				
Adverse events			X	X	X
Dispense/return	D	D/R	D/R	R	

Table 4. Frequency (Percent) of Adverse Events Related to Travoprost and Study Drugs

	Brimonidine (N = 79)		Brinzolamide (n = 84)	
Adverse Event	*Baseline*	*Follow-up*	*Baseline*	*Follow-up*
Allergy	1 (1.3%)	6 (7.6%) [1]	1 (1.2%)	7 (8.5%) [2]
Blurred vision	0	0	1 (1.2%)	1 (1.2%)
Conjunctivitis	0	1 (1.3%)	1 (1.2%)	0
Dizziness	0	1 (1.3%) [1]	1 (1.2%)	1 (1.2%)
Eye pain	2 (2.5%)	11 (14.0%) [1]	2 (2.4%)	5 (6.0%)
Gastrointestinal discomfort	0	0	0	1 (1.2%)
Headache	0	2 (2.5%)	0	1 (1.2%)
Hyperemia	2 (2.5%)	4 (6.3%) [1]	2 (2.4%)	4 (4.8%)
Lid pigment	0	0	0	1 (1.2%)
SPK	2 (2.5%)	0	2 (2.4%)	1 (1.2%)
Tearing	0	0	1 (1.2%)	0
Taste disturbance	0	0	0	2 (2.4%)
Uncontrolled IOP	0	2 (2.5%) [2]	0	1 (1.2%) [1]
Total	7	27	11	25

IOP = intraocular pressure; SPK = superficial punctate keratopathy.
[n], no. of patients who discontinued the study drug due to the specified adverse event.