Comparison of Topical Brinzolamide 1% and Dorzolamide 2% Eye Drops Given Twice Daily in Addition to Timolol 0.5% in Patients With Primary Open-angle Glaucoma or Ocular Hypertension

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• PURPOSE: **The aim was to compare topical brinzolamide 1% twice daily with dorzolamide 2% twice daily, each given with timolol 0.5% twice daily, for safety and effects on intraocular pressure in patients with primary open-angle glaucoma or ocular hypertension.**

• METHODS: **This double-blind, randomized, active controlled, parallel group study was conducted multinationally at 31 sites, in 241 patients as above, with assessments at baseline and monthly during 3 months of treatment. The primary end point was a diurnal reduction of trough/peak intraocular pressure from a timolol 0.5% twice daily baseline.**

• RESULTS: **Both treatment regimens reduced intraocular pressure significantly at all time points ($P < .001$): brinzolamide plus timolol by −3.6 to −5.3 mm Hg (−14.2 to −21.9%), dorzolamide plus timolol by −3.6 mm Hg to −5.1 mm Hg (−14.1 to −21.2%). Clinically relevant intraocular pressure reductions (decreases 5 mm Hg or greater or absolute intraocular pressure values 21 mm Hg or less) were manifested by 50.0% to 89.3% of patients under brinzolamide plus timolol and by 43.9% to 85.4% under dorzolamide plus timolol. The treatments were equivalent in mean intraocular pressure-lowering. In general, both regimens were well tolerated. However, more patients ($P = .001$) experienced at least one adverse event with dorzolamide plus timolol (32.8%) as compared with brinzolamide plus timolol (14.7%); also, more patients ($P = .001$) experienced ocular discomfort (stinging and burning) after dorzolamide plus timolol (13.1%) than after brinzolamide plus timolol (1.7%).**

• CONCLUSIONS: **In terms of intraocular pressure reduction, brinzolamide 1% twice daily was equivalent to dorzolamide 2% twice daily, each added to timolol 0.5% twice daily, but brinzolamide produced significantly less ocular burning and stinging. (Am J Ophthalmol 2001; 132:235–243. © 2001 by Elsevier Science Inc. All rights reserved.)**

THE TOPICAL USE OF CARBONIC ANHYDRASE INHIBITORS awaited the discovery of two new sulfonamide classes with high ocular penetration. The first new class, discovered in the late 1980s, comprised the heteroaromatic sulfonamides MK-927,[1,2] MK-417 (sezolamide),[3] and M-507[3] (dorzolamide), first marketed in 1995 in the United States as TRUSOPT (Merck and Company, Inc, Whitehouse, New Jersey). The topical efficacy of dorzolamide 2% three times daily was equivalent to betaxolol 0.5% twice daily in reducing the intraocular pressure of patients with open-angle glaucoma or ocular hypertension,[4] but both treatments were less effective than timolol 0.5% twice daily.[5] The second novel class of topical carbonic anhydrase inhibitor drugs (heterocyclic thienothiazine sulfonamides) is represented by brinzolamide, first marketed in 1998 in the United States and registered in the European Union as AZOPT (Alcon Laboratories, Inc, Fort Worth, Texas). The topical efficacy of brinzolamide (1% ophthalmic suspension) twice daily was equivalent to that of brinzolamide 1% three times daily, or dorzolamide 2% three times daily, whereas all three treatments were inferior to timolol 0.5% twice daily.[6] In a subsequent study, the addition of brinzolamide 1% three times daily to timolol 0.5% twice daily was clinically

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and statistically superior, throughout 3 months, to a similar regimen of placebo plus timolol.[7]

The prevalence of adverse effects after dorzolamide treatment appears to differ from brinzolamide. In particular, such ocular adverse effects as burning or stinging on instillation were reported in 43.9% of patients treated with dorzolamide in monotherapy over a 2-year clinical study,[8] as compared with 6.9% receiving brinzolamide 1% in monotherapy over an 18-month trial.[9] Such side effects can militate against treatment compliance.

The present study compared brinzolamide 1% twice daily with dorzolamide 2% twice daily, each given with timolol 0.5% twice daily, in terms of safety and effects on intraocular pressure in patients with primary open-angle glaucoma or ocular hypertension. The dorzolamide regimen was that previously recommended for adjunctive use with timolol.[10,11]

METHODS

THIS WAS A DOUBLE-BLIND, RANDOMIZED, ACTIVE-CONtrolled, parallel group study conducted multinationally at 31 sites according to a double-masked, randomized, parallel group design. Patients of either sex and any race were eligible if at least 21 years old and diagnosed with primary open-angle glaucoma (with or without pseudoexfoliation or pigment dispersion) or ocular hypertension uncontrolled by timolol 0.5% twice daily. A further stipulation was for intraocular pressure values between 23 to 36 mm Hg in at least one eye at 9 AM (before the morning dose of timolol 0.5%), and between 21 to 36 mm Hg in the same eye at 11 AM (after timolol), with no more than 5 mm Hg ocular difference at either time on both of two eligibility visits. In addition, a negative result of urinary pregnancy testing was required before treatment for all women of childbearing potential. The study was approved by the appropriate institutional review boards/independent ethics committees, and written informed consent was obtained from each patient.

Patients with other forms of glaucoma or any of the following ophthalmic conditions were excluded from the study: legal blindness; loss of sight in either eye; best-corrected Snellen visual acuity worse than 20/80 in either eye, or amblyopia; severe retinal disease or other pathology (for example, glaucomatous damage with a cup-to-disk ratio greater than 0.8, split fixation, or clinically significant field loss in the central 20 degrees); eye infection or laser surgery in the preceding 3 months; ocular trauma in the preceding 6 months; intraocular surgery in the preceding 12 months; a history of chronic or recurrent inflammatory eye disease; corneal abnormalities preventing reliable applanation tonometry; and an inability to discontinue contact lenses for the study duration. Also, patients with other conditions were excluded, as follows: pregnant or nursing women; history of hematologic disorders other than mild anemia; clinical evidence of electrolyte, renal, or hepatic abnormalities; severe or uncontrolled cardiovascular disease; clinically significant bradycardia or pulmonary disease that would preclude the use of an ophthalmic β blocker; and known serious or severe hypersensitivity to timolol, carbonic anhydrase inhibitors, sulfonamides, or components of such medications. Lastly, patients were excluded if they took medications, as follows: current corticosteroid treatments of any kind; systemic drugs that might affect intraocular pressure (for example, autonomic agents), but not those taken regularly for more than 1 month; or investigational drugs during the preceding 30 days.

At the initial screening visit, all previous ocular hypotensive medication was discontinued. Timolol 0.5% ophthalmic solution twice daily was started (open-label) and maintained throughout the study. After a 3-week run-in period with timolol 0.5% twice daily, ocular measurements were repeated during two eligibility visits 1 week apart. Patients became eligible when they met the intraocular pressure criteria (specified earlier) on both visits. They were then assigned to dose both eyes with either brinzolamide 1% ophthalmic suspension twice daily (AZOPT; Alcon Laboratories, Inc, Fort Worth, Texas) or dorzolamide 2% ophthalmic solution twice daily (TRUSOPT; Merck and Company, Inc, Whitehouse, New Jersey) for 3 months. The study was double-masked so that patients, investigators, and the study sponsor staff were unaware of individual patient's treatments or codes. Investigators were given sealed envelopes containing a description of the test material for each patient, in case of emergencies. All envelopes were returned to Alcon at the end of the study. Treatments were similar in taste, appearance, and packaging, using opaque DROP-TAINERs (Alcon Laboratories, Inc, Fort Worth, Texas) with labels numbered for each patient.

Patients were instructed to continue with topical timolol 0.5% at 9 AM and 9 PM in both eyes, and to instill one drop of the trial medication in both eyes 5 to 10 minutes after timolol. Eligibility visits also provided baseline efficacy and safety measurements. The measurements were repeated at the end of each month for 3 months.

Several procedures were standardized throughout the study to minimize any confounding variables. In particular, intraocular pressure measurements were performed by the same individual at all study visits using Goldmann applanation tonometry at all sites.[12–14] Measurements were made during the diurnal morning increase of intraocular pressure,[15] with trough intraocular pressure measured before treatment at 9 AM, approximately 12 hours after the previous medication and peak intraocular pressure at 11 AM, approximately 2 hours after the morning treatment. Two intraocular pressure measurements were made for each eye and averaged if the values differed by 4 mm Hg or less. Otherwise a third measurement was taken and the two closest values were averaged. If all three values differed by

the same amount, all three were averaged. Averages were rounded up to the nearest integer.

The measurement procedure above was repeated for both eyes. If the intraocular pressure for each eye differed by more than 5 mm Hg, both eyes were considered unevaluable for efficacy. In the per protocol data set, one eye was determined to be evaluable for efficacy if it was between 23 and 36 mm Hg inclusive at 9:00 AM and between 21 and 36 mm Hg inclusive at 11:00 AM. These criteria were required to be met in the same eye on both eligibility examinations days. If both eyes were considered evaluable at baseline, the intraocular pressure was the average of the two values during all follow-up visits. If only one eye met the baseline criteria, then only data from that eye were used.

In the intent-to-treat analysis, intraocular pressure was the average of both eyes at all follow-up visits (that is, both eyes were considered evaluable in the intent-to-treat data set).

Baseline intraocular pressure was the average of the intraocular pressure measurements for the evaluable eyes across both eligibility examinations days. Change from baseline was the diurnally corrected change from this average baseline.

Ocular safety assessments on all visits comprised Snellen visual acuity (best corrected) and ocular signs scored for eyelid, conjunctiva, and slit-lamp (biomicroscopy) features (cornea, iris/anterior chamber, lens, vitreous). Dilated ophthalmoscopy was performed at the screening visit and month 3 to assess fundus features (retina, macula, choroid, optic nerve, and disk pallor) and to measure the cup-to-disk ratio. Visual fields, measured by automated perimetry using generally a Humphrey Field Analyzer (Zeiss Humphrey Systems, Dublin, California) or Octopus Perimeter (Haag-Streit, Mason, Ohio) and pupil diameter measurements were performed at the second eligibility visit and month 3. Resting pulse rate, blood pressure, and adverse events were recorded on all visits.

Treatment equivalence was declared if the 95% confidence limit (two sided) for the between-group difference in intraocular pressure reduction from the diurnal baseline was less than 1.5 mm Hg, assuming a standard deviation of 3.4 mm Hg. The power of the study to detect such a difference was greater than 80% with 110 evaluable patients per group.

The primary efficacy comparison was restricted to patients who met the criteria for inclusion and exclusion and the evaluability criteria, but an intent-to-treat analysis was also performed on all evaluated patients. Baseline intraocular pressure values were averages per eye and hour on both evaluation visits. Change from baseline was related to the corresponding eye and hour. The last observation value was carried forward when patients were withdrawn for treatment failure, defined as intraocular pressure inadequately controlled in the investigator's judgment.

A repeated measures analysis of variance model was used to estimate treatment differences and confidence intervals for intraocular pressure reductions from baseline. Tabulated values are least-square means. Time-of-day treatment means were combined over months if there were no significant treatment *x* month interactions ($\alpha = 0.1$). Tests were also performed to verify homogeneity between centers and investigators. The estimate was based on the difference in means, the treatment nested within investigator effect, and patient nested within the treatment by investigator interaction effect.

Baseline data for the visual safety variables related to either the screening visit (dilated fundus features, cup-to-disk ratio) or the second evaluation visit at 9 AM (visual acuity, ocular signs, visual field, and pupil diameter). Both eyes of patients were included in all safety analyses.

Treatments were compared with the following tests: Cochran-Mantel-Haenszel test for changes of visual acuity (largest Snellen decrease at month 3 − baseline); chi-squared test for changes of fundus features (month 3 − baseline) and ocular sign scores (worst score − baseline); and one-way analysis of variance for changes of cup-to-disk ratio (month 3, 11 AM − baseline), visual field variables (Humphrey method: mean deviation and corrected pattern standard deviation; Octopus method: mean defect and corrected loss variance; month 3, 9 AM − baseline), and pupil diameter (month 3, 9 AM − baseline).

Blood pressure and pulse rate changes (month 3 − second eligibility visit) were analyzed by a repeated measures analysis of variance.

RESULTS

IN TOTAL, 241 PATIENTS WERE RANDOMIZED TO EITHER treatment at 31 centers in 13 countries. All except three patients, that is, 238 patients, received at least one dose of a trial drug and were therefore evaluated in both the safety analysis and intent-to-treat efficacy analysis. Intraocular pressures at eligibility were too low in the three cases not treated.

Twenty-eight patients were ineligible for the primary efficacy analysis because of serious protocol deviations. These included 14 patients treated with brinzolamide plus timolol and 14 with dorzolamide plus timolol. Reasons for exclusion were as follows: nonqualifying intraocular pressure (n = 7), intraocular pressure asymmetry (n = 16), one eye not treated (n = 2), and neither eye treated (n = 3, above). No significant difference was found in reasons for exclusion between treatment groups. This left 213 patients eligible for the baseline primary efficacy analysis. Patient numbers are shown in the adjacent flow chart (Table 1).

A total of 15 patients discontinued from the study, of which seven were treated with brinzolamide plus timolol and eight with dorzolamide plus timolol. Reasons for discontinuation were as follows: adverse events (n = 6), inadequate control of intraocular pressure (n = 2), patient

TABLE 1. Trial Design and Patient Numbers (N/n)

Randomized to Treatments	Evaluated for Safety	Evaluated for Efficacy (Intent-to treat)*							
		Baseline		Month 1		Month 2		Month 3	
		9 AM†	11 AM‡	9 AM†	11 AM‡	9 AM†	11 AM‡	9 AM†	11 AM‡
Brinzolamide§ (118)	Brinzolamide§ (116)	104	104	104	104	103	103	101	102
Dorzolamide§ (123)	Dorzolamide§ (122)	109	107	107	106	105	105	105	103

*Number of patients with valid measurement at each time point.
†Pretimolol measurements.
‡Posttimolol measurements.
§Plus timolol.

TABLE 2. Patient Demography

Parameter	Brinzolamide + Timolol		Dorzolamide + Timolol		*P* Value*
	n 104	%	n 109	%	
Age					
<65 years	52	50.0	45	41.3	.202
≥65 years	52	50.0	64	58.7	
Sex					
Male	54	51.9	48	44.0	.249
Female	50	48.1	61	56.0	
Race					
Caucasian	99	95.2	108	99.1	.086
Other	5		1		
Iris color					
Blue	31	29.8	26	23.9	.760
Brown	45	43.3	46	42.2	
Other	28	26.9	37	33.9	
Diagnosis					
POAG†	59	56.7	69	63.3	.032
OH‡	38	36.5	33	30.3	
PDG§	5		0		
PsG‖	2		7		

*Chi-square test of independence.
†Primary open-angle glaucoma.
‡Ocular hypertension.
§Pigment dispersion glaucoma.
‖Pseudoexfoliative glaucoma.

decision (n = 2), intraocular pressure below entry criterion (n = 4), and intraocular pressure asymmetry (n = 1). Five of the discontinued patients were also excluded from the primary efficacy analysis for reasons stated earlier.

The demography of the two treatment groups is shown in Table 2. The only significant difference was a higher proportion of patients with ocular hypertension treated with brinzolamide plus timolol than with dorzolamide plus timolol. The different proportions were unlikely to have clinical relevance.

The efficacy of both treatment regimens in reducing intraocular pressure is shown in Table 3 and Figure 1 where brinzolamide reduced intraocular pressure by −3.6 to −4.6 mm Hg (−14.2 to −17.1%) at trough (9 AM) and by −4.9 to −5.3 mm Hg (−19.9 to −21.9%) at peak (11 AM) relative to the timolol baseline; dorzolamide did likewise, by −3.6 to −4.3 mm Hg (−14.1 to −16.6%) at trough and by −4.6 to −5.1 mm Hg (−19.1 to −21.2%) at peak. The effects of both regimens were statistically significant at all time points ($P < .001$). The clinical relevance of the intraocular pressure reductions in Table 3 was supported by a posthoc analysis that compared the percentage of patients under each regimen whose response to treatment was either an intraocular pressure reduction 5 mm Hg or greater or an absolute intraocular pressure 21 mm Hg or less. The proportion of patients satisfying the criteria ranged from 50.0% to 89.3% under brinzolamide plus timolol, and from 43.9% to 85.4% under dorzolamide plus timolol (Table 4 and Figure 2).

The treatments were equivalent in efficacy, as shown in Table 3, where intraocular pressure reductions differed nonsignificantly by 0.5 mm Hg or less at all time points, and by the 95% confidence intervals for differences between treatment means, which all fell within ± 1.0 mm Hg, ranging from ± 0.31 mm Hg to ± 0.90 mm Hg. Further support for equivalence was obtained by analyzing data pooled for each time of day across visits (a valid procedure in the absence of a treatment–visit interaction) to maximize statistical power and reduce error inherent in repeated measurements (not shown). Treatment effects were again similar at both 9 AM ($P = .462$) and 11 AM ($P = .974$).

The reported treatment equivalence in intraocular pressure reduction remained unchanged when possible demographic, investigator, or center effects were analyzed and when the intent-to-treat analysis was performed. The differences between treatments were homogeneous among sites. The overall treatment difference was 0.14 mm Hg, favoring brinzolamide plus timolol over dorzolamide plus timolol. Four of the 31 investigators had only one evaluable patient, so a treatment difference could not be calculated. Twenty-five of the remaining 27 sites had mean treatment differences that fell within 1.5 mm Hg of the overall mean difference (0.14 mm Hg), indicating 93% of

TABLE 3. Treatment Effects on Intraocular Pressure

	Baseline		Change From Respective Baseline by Visit and Time of Day					
			Month 1		Month 2		Month 3	
	9 AM	11 AM	9 AM	11 AM	9 AM	11 AM	9 AM	11 AM
brinzolamide + timolol								
mm Hg	25.5	24.1	−3.6	−4.9	−4.6	−5.3	−4.3	−4.9
SD	1.9	2.0	3.0	2.6	3.2	2.4	2.9	2.9
n	103	104	104	104	103	103	101	102
dorzolamide + timolol								
mm Hg	25.8	24.1	−3.6	−4.6	−4.1	−5.1	−4.3	−5.0
SD	2.2	1.9	2.6	2.4	2.9	2.4	3.1	2.5
n	109	109	107	106	105	105	105	103
P Value	.329	.799	.968	.423	.249	.660	.893	.703
Delta (brinzolamide − dorzolamide)								
mm Hg	—	—	0.0	−0.3	−0.4	−0.2	−0.1	0.2
95% Confidence interval (upper)	—	—	0.73	0.44	0.31	0.58	0.70	0.90

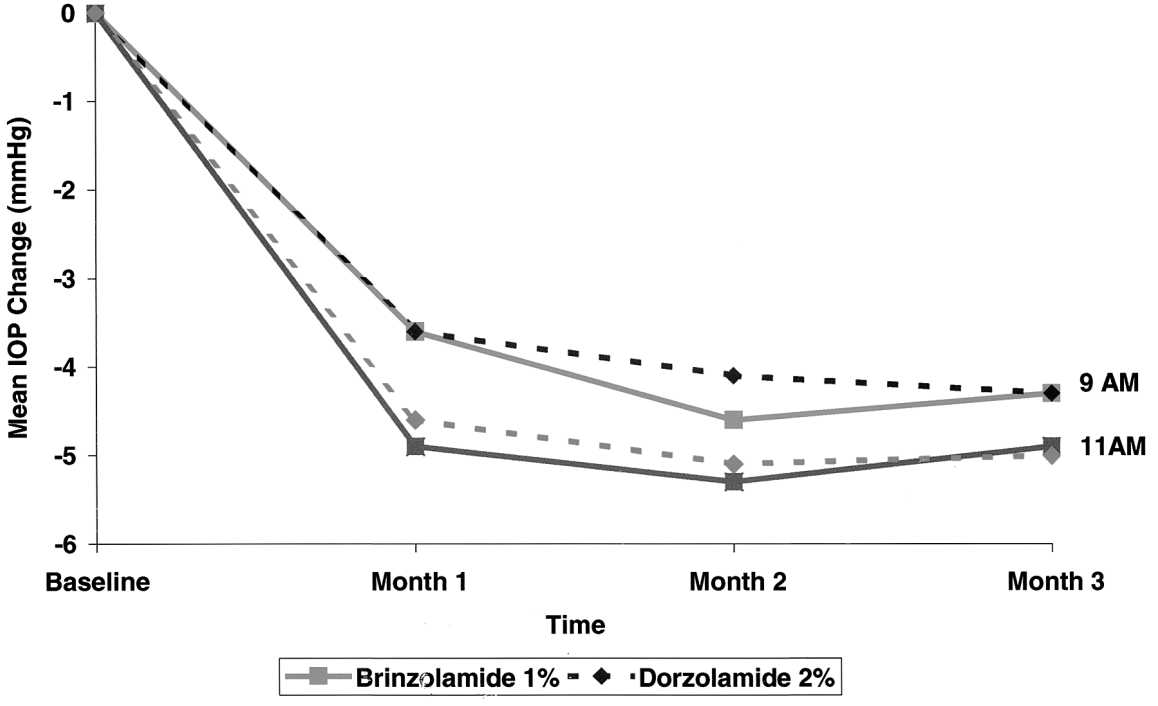

FIGURE 1. Mean intraocular pressure changes from a timolol 0.5% alone baseline. Trough values (9:00 AM) and peak values (11:00 AM).

the investigators produced treatment differences that were clinically similar to the overall treatment difference. Two sites produced treatment differences that favored brinzolamide over dorzolamide. These sites had only two and three evaluable patients, respectively.

Treatment compliance could not be estimated with any accuracy, because the amount of fluid used from the quantity dispensed relied on the instillation technique. However, gross noncompliance would have resulted in either a return of virtually unused medication or more patients withdrawn because of inadequate intraocular pressure control. Neither was the case. One patient only was withdrawn from each group because of inadequate intraocular pressure control.

The analysis of all adverse events showed that 17 patients (14.7%) treated with brinzolamide plus timolol experienced adverse events as compared with 40 patients (32.8%) treated with dorzolamide plus timolol ($P = .001$, Fisher's exact test).

Five patients experienced seven ocular adverse events

TABLE 4. Percent of Patients With Clinically Relevant* Intraocular Pressure Reductions

Treatment	Month 1		Month 2		Month 3	
	9 AM	11 AM	9 AM	11 AM	9 AM	11 AM
brinzolamide + timolol						
%	50.0	83.7	67.0	89.3	61.4	81.4
n	104	104	103	103	101	102
dorzolamide + timolol						
%	43.9	73.6	55.2	83.8	59.0	85.4
n	107	106	105	105	105	103

*Intraocular pressure decreases ≥ 5 mm Hg or absolute intraocular pressure values ≤ 21 mm Hg.

attributed to brinzolamide plus timolol, as compared with 26 patients and 34 events related to dorzolamide plus timolol. Adverse events with an incidence of 1.0% or greater are shown in Table 5. Ocular discomfort (stinging and burning) was significantly less frequent with brinzolamide plus timolol than dorzolamide plus timolol ($P = .001$, Fisher's exact test). Four patients treated with dorzolamide plus timolol were withdrawn from the study because of seven ocular adverse events, as follows: burning (2), unspecified cataract (1), decreased vision (1), blurred vision (1), blepharitis (1), and keratoconjunctivitis (1). In general, however, ocular adverse events related to therapy were nonserious and mild to moderate in severity. They usually resolved without treatment and did not interrupt the study.

Other adverse events related to treatment affected five patients under brinzolamide plus timolol (five events) and five patients under dorzolamide plus timolol (five events). Taste perversion was the only event to attain an incidence 1.0% or greater (Table 5). One patient treated with brinzolamide plus timolol was withdrawn from the study because of severe pneumonia with acute cardiorespiratory distress and asthma, attributed to timolol.

Changes from the timolol baseline of visual acuity, ocular signs, dilated fundus features, cup-to-disk ratio, visual fields, pulse, or blood pressure did not differ significantly between the treatment groups.

DISCUSSION

THE SIGNIFICANCE OBSERVED ACROSS DIAGNOSIS GROUPS in the demographic data is probably an artifact of the sparse number of patients for the pigmentary and pseudoexfoliation subgroups. If these two subgroups are lumped together with primary open-angle glaucoma, then the percentages are 36.5% ocular hypertension and 63.5% primary open-angle glaucoma in brinzolamide and 30.3% ocular hypertension and 69.7% primary open-angle glaucoma in dorzolamide, with a P value of .3324 for the treatment group comparison of these two distributions. The observed difference has therefore most likely no clinical consequence on the study results.

This study demonstrated that a twice-daily regimen of topical brinzolamide 1% plus timolol 0.5% reduced morning intraocular pressure values by −14.2 to −21.9% for a period of 3 months, relative to the timolol baseline. The effect was slightly larger than that of a smaller study in which a regimen of brinzolamide 1% three times daily plus timolol 0.5% twice daily reduced similar intraocular pressure measurements by −13.2 to −16.6%.[7] Likewise, in the present study, twice-daily dorzolamide 2% plus timolol 0.5% reduced intraocular pressure values by −14.1 to −21.2% from baseline. The latter result was consistent with morning intraocular pressure reductions of −16.8 to −21.0% after 8 days of treatment with dorzolamide 2% twice daily plus timolol 0.5% twice daily,[10] but was greater than observed (−13 to −14%) after 2 weeks of treatment, and maintained for 6 months in another study reported in the same publication.[10] In the present study, intraocular pressure reductions were statistically significant. This was confirmed by the proportion of patients at each visit who met an established clinical response criterion (brinzolamide plus timolol, 50% to 89%; dorzolamide plus timolol, 44% to 85%). The comparison of the present study with the brinzolamide 1% three times daily trial discussed above confirms that there is no clinical benefit offered by three times daily dosing with brinzolamide 1% when given adjunctively to timolol 0.5%, compared with the approved twice daily indication for this product. The twice daily dosing regimen is also approved in this indication for dorzolamide 2%. In fact, the results presented in Table 3 and illustrated in Figure 1 suggest an adequate residual intraocular pressure–lowering efficacy at the 9 AM trough, 12 hours after the evening instillation (approximately 15% for both treatment groups). Additionally, it must be noted that the 9 AM intraocular pressure measurement was also occurring at the time of the morning intraocular pressure peak,[15] which placed both study medications in worst-case conditions.

The subgroup analyses and the test of homogeneity of efficacy among investigators did not show differences. This reflects no interobserver meaningful variation in equipment, testing procedures, or severity of disease.

A further perspective on the above results would be given by contrasting topically and orally administered carbonic anhydrase inhibitors in terms of intraocular pressure reduction. A direct comparison was made in one study[16] in which dorzolamide 2% twice daily administered for 3 months in addition to timolol 0.5% twice daily produced intraocular pressure reductions of approximately 16%, whereas acetazolamide tablets 250 mg four times daily produced intraocular pressure reduction of approximately 18%. Although the intraocular pressure–lowering effect of acetazolamide appeared marginally greater than

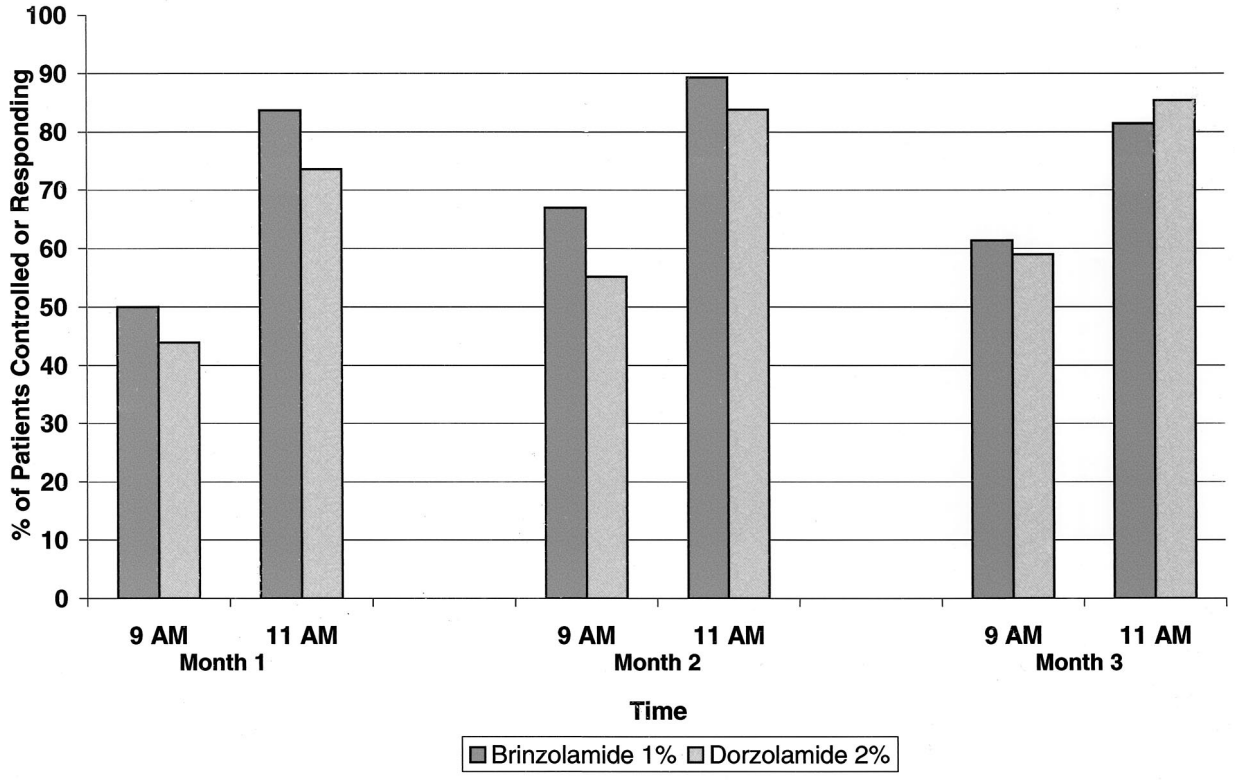

FIGURE 2. Percents of patients controlled (intraocular pressure 21 mm Hg or less) or responding (intraocular pressure reduction 5 mm Hg or greater) to treatment.

TABLE 5. Incidence of Treatment-related Adverse Events With Greater Than 1% Frequency

	Brinzolamide + Timolol		Dorzolamide + Timolol	
Adverse Event	n 116	%	n 122	%
Ocular				
Discomfort	2		16	13.1
Hyperemia			4	
Tearing			3	
Pruritus			2	
Blurred vision	2		2	
Other				
Taste perversion	3		4	

that of dorzolamide, its tolerance was significantly poorer. It would seem that a similar magnitude of intraocular pressure reductions was achieved in the current study with topical brinzolamide or dorzolamide added to the timolol regimen.

This study is the first to compare, directly, the effects on intraocular pressure reduction of topical brinzolamide 1% and dorzolamide 2%, when given in conjunction with timolol 0.5%. The results showed clinical and statistical equivalence of the two treatments, in terms of intraocular pressure changes from baseline, at every visit during 3 months of treatment. Indeed, mean intraocular pressures never differed between groups by more than 0.5 mm Hg. This was much less than the normal intraocular pressure variation with repeated Goldmann tonometry and therefore probably not clinically important.[12–14] Likewise, other measures that reveal the progression of glaucoma (dilated fundus and visual field examinations) did not distinguish between the groups, but the duration of the study can be considered too short to evidence such changes. Equivalent reductions of intraocular pressure were also found with brinzolamide 1% twice daily or three times daily and dorzolamide 2% three times daily, given as monotherapy.[6]

In contrast to similar efficacy of brinzolamide 1% twice daily and dorzolamide 2% three times daily, the introduction noted a much higher incidence of some adverse events associated with dorzolamide monotherapy. These observations were confirmed by the present study, which compared adverse effect frequencies when the treatments were given as adjuncts to timolol therapy. The overall incidence of patients experiencing adverse events was significantly higher with dorzolamide plus timolol (32.8%) than brinzolamide plus timolol (14.7%) and, likewise, more patients complained of ocular discomfort after dorzolamide plus timolol (13.1%) than after brinzolamide plus timolol (1.7%). Furthermore, four patients discontinued from the

study because of dorzolamide-related ocular effects related to local tolerance (burning/stinging, blepharitis, keratoconjunctivitis) but none of the brinzolamide-treated patients. The latter result is supported by two studies that used a five-point rating scale to quantify discomfort and found significantly more discomfort, and more patients reporting discomfort, after dorzolamide 2% three times daily than brinzolamide 1% three times daily.[17] In other respects both treatments of the present study were generally well tolerated. Adverse events relating to therapy were generally mild to moderate and usually resolved without other treatment or interruption to the study medication.

Although brinzolamide 1% twice daily was equivalent in efficacy to dorzolamide 2% twice daily, when added to timolol 0.5% twice daily, the far fewer complaints of discomfort after brinzolamide instillations might well encourage treatment compliance under more typical practice conditions.[18] Although the present study was not specifically evaluating the relation between ocular tolerance of medications and patients' compliance, this could be important, as poor treatment compliance with glaucoma treatment can engender serious consequences.

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