The Long-term Safety and Efficacy of Brinzolamide 1.0% (Azopt) in Patients With Primary Open-angle Glaucoma or Ocular Hypertension

WAYNE F. MARCH, MD, KATHERINE I. OCHSNER, MD, AND THE BRINZOLAMIDE LONG-TERM THERAPY STUDY GROUP

• PURPOSE: Oral carbonic anhydrase inhibitors used to treat glaucoma have significant systemic side effects. Brinzolamide 1.0%, a new topical ocular carbonic anhydrase inhibitor, is effective apparently without significant systemic side effects. This study was performed to establish the long-term safety and efficacy of brinzolamide 1.0% two and three times daily for primary open-angle glaucoma and ocular hypertension.

• METHODS: An 18-month, multicenter, double-masked, parallel, controlled study was conducted. Patients were randomized to brinzolamide two or three times daily or timolol 0.5% twice daily in a 2:2:1 ratio (n = 150, 153, and 75, respectively). Intraocular pressure was measured at 8:00 AM at eligibility and months 1, 3, 6, 9, 12, 15, and 18. Efficacy was based on intraocular pressure reduction from baseline. Safety was also evaluated.

• RESULTS: All regimens produced clinically relevant and statistically significant ($P < .05$) intraocular pressure reductions from baseline. Mean changes in intraocular pressure trough measurements ranged from −2.7 to −3.9 mm Hg with brinzolamide twice-daily dosing and −2.8 to −3.8 mm Hg three times daily dosing compared with −4.7 to −5.6 mm Hg with timolol. The intraocular pressure reductions with brinzolamide two and three times daily were clinically and statistically equivalent. One hundred forty-four patients were discontinued from the study after randomization with the most common reasons being the occurrence of an adverse event (46), inadequate intraocular pressure control (23), patient decision unrelated to study medication (11), lost to follow-up (16), and noncompliance (9). Adverse events were nonserious and resolved without sequelae. There were no clinically relevant changes in safety parameters. Brinzolamide produced less ocular discomfort (burning/stinging) than timolol, and total carbonic anhydrase inhibition levels remained below that known to cause systemic side effects.

• CONCLUSION: Brinzolamide produced significant and equivalent reductions in intraocular pressure when dosed two and three times daily for 18 months. Brinzolamide was safe and well tolerated by patients, with minimal ocular discomfort. (Am J Ophthalmol 2000;129: 136–143. © 2000 by Elsevier Science Inc. All rights reserved.)

Accepted for publication Sept 3, 1999.

From the University of Texas Medical Branch, Galveston, Texas.

This research was supported by an unrestricted grant from Research to Prevent Blindness, New York, New York. The study was funded by Alcon Laboratories, Inc, Ft Worth, Texas.

Reprint requests to Wayne F. March, MD, Department of Ophthalmology and Visual Sciences, The University of Texas Medical Branch, 700 University Blvd, Galveston, TX 77550; fax: (409) 747-5812; e-mail: wfmarch@utmb.edu

ORAL CARBONIC ANHYDRASE INHIBITORS HAVE played an important role in the treatment of glaucoma since their introduction.[1] Intraocular pressure reduction is produced by suppression of aqueous humor formation resulting from inhibition of bicarbonate secretion into the posterior chamber by the ciliary epithelium.[2] The problem with using oral carbonic anhydrase inhibitors for intraocular pressure control has been the significant systemic side effects associated with generalized inhibition of carbonic anhydrase.

These side effects may be reduced or eliminated with topical application. Developing a topically active form of carbonic anhydrase inhibitors has been difficult, however. Few agents have been able to penetrate the cornea without affecting its hydration and function while at the same time significantly reducing aqueous production and intraocular pressure. Forty years after the introduction of oral carbonic anhydrase inhibitors, the first topically active carbonic anhydrase inhibitor, dorzolamide 2.0%, became commercially available for the treatment of glaucoma.[3]

0002-9394/00/$20.00
PII S0002-9394(99)00343-8

Brinzolamide 1.0% (Azopt; Alcon Laboratories, Inc, Ft Worth, Texas) is a new topical carbonic anhydrase inhibitor that has proven to be safe and well tolerated while significantly lowering intraocular pressure in the short term.[4,5] The purpose of the study reported here was to evaluate the long-term safety and efficacy of brinzolamide 1.0% two and three times daily in patients with primary open-angle glaucoma and ocular hypertension.

METHODS

THE STUDY WAS A MULTICENTER, DOUBLE-MASKED, PRIMARY therapy trial designed to evaluate the safety and efficacy of brinzolamide 1.0% ophthalmic suspension two and three times daily. Timolol 0.5% (Timoptic, Merck and Company, Inc) ophthalmic solution twice daily was included as a therapeutic reference standard. The primary efficacy parameter was intraocular pressure reduction from baseline. Safety was assessed through the evaluation of adverse events, visual acuity, biomicroscopic examinations, pulse, blood pressure, corneal endothelial cell density, corneal thickness, laboratory blood chemistry, hematology, and urinalysis evaluations. In addition, whole blood brinzolamide concentrations and red blood cell carbonic anhydrase activity were monitored in patients at randomly selected study sites. The same patients were used for these evaluations throughout this study.

To be enrolled in the study, patients had to be at least 21 years of age of any race and either gender diagnosed with primary open-angle glaucoma or ocular hypertension. Patients were excluded from the study if they had amblyopia, only one sighted eye or visual acuity worse than 20/80 in either eye, a history of chronic or recurrent inflammatory eye disease, severe retinal disease, or other severe ocular pathology. Patients who had undergone ocular surgery within the past 12 months or laser surgery within the past 3 months were also excluded. Patients had to discontinue contact lens wear during the study and could not use any steroids. Women who were pregnant or nursing were excluded. Patients with a history of hypersensitivity to any component of the test medications were also excluded. Patients using any systemic medications that would affect intraocular pressure had to be on a stable dosing regimen for at least 1 month before the screening visit.

The study was 18 months in duration and had two phases, a run-in and a masked treatment phase. Before the run-in phase, patients signed an informed consent form that had been reviewed and approved by an independent Institutional Review Board and were initially screened for inclusion and exclusion criteria. At the screening visit, medical and medication history and demographic information were recorded. Snellen visual acuity, biomicroscopy, dilated fundus examinations, and gonioscopy were conducted. Resting heart rate and blood pressure were measured, and a pregnancy test was conducted for all women of child-bearing potential. Eligible patients entered the run-in phase of the study, during which all ocular hypertensive medications were discontinued as follows: at least 3 weeks for topical β blockers, at least 2 weeks for sympathomimetics or α agonists, at least 5 days for miotics, and at least 5 days for topical or oral carbonic anhydrase inhibitors.

After washout, patients returned for the 8:00 AM eligibility examination. The examination included visual acuity and biomicroscopy examination, intraocular pressure measurement using Goldmann applanation tonometry, blood pressure, and resting pulse measurements. Only patients with an intraocular pressure of 22 to 36 mm Hg, inclusive in at least one eye, and an intraocular pressure difference of 5 mm Hg or less between eyes qualified to continue in the study. Blood and urine samples were collected for a complete blood count, blood chemistry, and urinalysis. Patients with any evidence of clinically significant hematologic, electrolyte, renal, or hepatic abnormalities based on the laboratory results were not allowed to continue in the study. Baseline central corneal thickness measurements, endothelial cell density photographs, and automated perimetry were also obtained at the eligibility visit. In addition, whole blood samples were collected from patients at selected sites to obtain baseline values for brinzolamide concentrations and carbonic anhydrase inhibitor activity.

Patients who met all entry qualifications entered the masked treatment phase of the study. They were randomized to receive either brinzolamide 1.0% twice daily, brinzolamide 1.0% three times daily, or timolol 0.5% twice daily in a 2:2:1 ratio. Masking for the two and three times daily dosing regimens was maintained by providing each patient with three masked bottles labeled "morning," "afternoon," and "nighttime." Patients on the three times daily regimen had active medication in all three bottles. Patients on the twice-daily regimens had active medications in the morning and nighttime bottles and placebo in the afternoon bottle. The placebo contained the same components and was the same pH as the brinzolamide study drug without the active component, brinzolamide. Patients were instructed to instill one drop of study medication in each eye at 8:00 AM, 4:00 PM, and 10:00 PM from the corresponding bottle. Patients were scheduled to return for follow-up study visits at months 1, 3, 6, 9, 12, 15, and 18.

All visits were scheduled for 8:00 AM, before the morning dose of medication. At each scheduled visit, patients' predose (trough) intraocular pressure was measured. Other measurements included resting pulse and blood pressure and Snellen visual acuity. Biomicroscopy was also conducted. Complete blood count, blood chemistry, and urinalysis evaluations were conducted at months 3, 6, 12, 15, and 18. At month 9, a complete blood count was the only laboratory evaluation conducted. Corneal endothelial

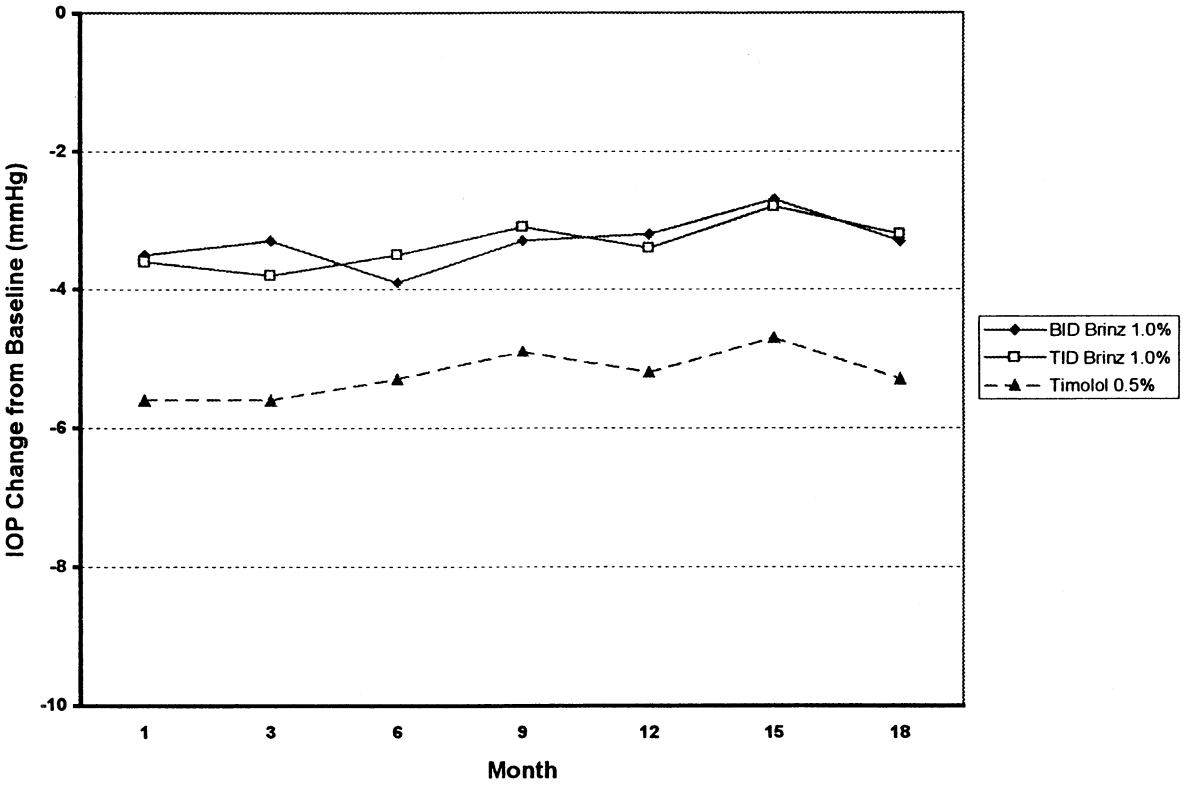

FIGURE 1. Mean change in intraocular pressure from baseline at each treatment visit.

cell photographs and central corneal thickness measurements were performed at months 6, 12, and 18. Automated perimetry and dilated fundus examinations were repeated at month 12 and on completion. At the sites selected for pharmacokinetic evaluations, whole blood samples were collected at months 3, 6, 9, 12, 15, and 18.

Patients meeting inclusion/exclusion criteria were invaluable for efficacy. The efficacy analysis was based on the mean change from baseline in intraocular pressure. An analysis of covariance model was used to estimate long-term effectiveness and intraocular pressure reductions. The primary comparisons were based on least squares means. The model was fit using PROC MIXED of SAS version 6.12 (SAS/STAT Software: Changes and Enhancements for Release 6.12; SAS Institute, Inc, Cary, North Carolina).

Long-term effectiveness was evaluated by determining that the mean intraocular pressure reduction from baseline was significantly different from zero with a 95% confidence interval about the mean. To demonstrate equivalence, the two and three times daily dosing regimens of brinzolamide were required to have a two-sided 95% confidence interval on the difference between treatments within ± 1.5 mm Hg. Comparisons of both brinzolamide dosing regimens to timolol 0.5% twice daily were also made using an analysis of covariance model.

Adverse events were defined as any change from baseline in a patient's ophthalmic or medical health during the course of the study and were obtained as solicited complaints or investigator observations and recorded by the investigator at each patient's visit. Endothelial cell density and central corneal thickness was analyzed using repeated measures analysis of variance of change from baseline. Change from baseline was calculated at months 6, 12, and 18 using the eligibility visit as baseline. For each patient, the average of the two eyes was used in the analysis. Laboratory values were analyzed using a one-way analysis of variance for change from baseline at month 18 compared with the eligibility visit baseline values.

RESULTS

AT 18 INVESTIGATIONAL SITES, 378 PATIENTS WERE RANdomized to treatment and were included in the safety and intent-to-treat analysis. There were no significant differences between treatment groups with respect to demographics ($P > .595$; Table 1). The primary efficacy group included 369 patients whose visits were determined to be invaluable for efficacy. One hundred forty-four patients were discontinued from the study after randomization with the most common reasons being the occurrence of an adverse event (46), inadequate intraocular pressure control

TABLE 1. Demographic Characteristics of Intent-to-Treat Patients

Characteristic	N	Treatment Group: BID Brinzol %	BID Brinzol N	TID Brinzol %	TID Brinzol N	Timolol 0.5% (%)	*P* Value*
Age (years)							
Mean ± SD	63 ± 11.6			60.3 ± 12.9		59.9 ± 13.2	.0595
<65	70	46.7	84	54.9	41	54.7	.299
>65	80	53.3	69	45.1	34	45.3	
Sex							
Male	68	45.3	76	49.7	28	37.3	.213
Female	82	54.7	77	50.3	47	62.7	
Race							
White	120	80.0	116	75.8	59	78.7	.889
Black	27	18.0	33	21.6	14	18.7	
Other	3	2.0	4	2.6	2	2.7	
Iris color							
Brown	78	52.0	84	54.9	40	53.3	.299
Hazel	20	13.3	24	15.7	6	8.0	
Green	4	2.7	3	2.0	5	6.7	
Blue	43	38.7	39	25.5	24	32.0	
Grey	5	3.3	3	2.0	—	—	
Diagnosis							
POAG	86	57.3	89	58.2	47	62.7	.977
OH	59	39.3	57	37.3	25	33.3	
Pigment	3	2.0	5	3.3	2	2.7	
Dispersion							
Pseudoexfoliation	2	1.3	2	1.3	1	1.3	

BID = two times daily; brinzol = brinzolamide; OH = ocular hypertension; POAG = primary open-angle glaucoma; TID = three times daily.
**P* values are from chi-square test of independence, except for comparison of mean age, which was analyzed by one-way analysis of variance for difference between groups.

(23), patient decision unrelated to study medication (11), lost to follow-up (16), and noncompliance (9) (Table 2).

There was a statistically significant difference ($P = .0288$) between the brinzolamide two and three times daily treatment groups with regard to mean baseline intraocular pressure values (mean twice-daily intraocular pressure = 25.1; mean three times daily intraocular pressure = 26.1). Because of this difference, an analysis of covariance model was used to estimate mean intraocular pressure reductions to avoid bias introduced by differences in baseline intraocular pressure means.

Two and three times daily dosing with brinzolamide 1.0% measured before morning dosing produced clinically relevant and statistically significant reductions in intraocular pressure from baseline ($P < .0001$). These reductions were maintained over the 18-month treatment period. Two and three times daily dosing with brinzolamide 1.0% were found to be clinically and statistically equivalent. The results presented are from the efficacy analysis. These results are supported by the intent-to-treat analyses.

Intraocular pressure changes for brinzolamide from baseline ranged from −2.7 to −3.9 mm Hg twice daily and −2.8 to −3.8 mm Hg three times daily, and −4.7 to −5.6 for timolol twice daily (Figure 1). Changes from baseline were statistically significant ($P < .0001$) for all three groups at all visits (Table 3). Intraocular pressure reductions in both the two and three times daily brinzolamide treatment groups remained stable over the 18-month treatment period. Measurements of trough intraocular pressure over the course of the study showed that brinzolamide 1.0% twice daily produced an average reduction of 3.3 mm Hg, 1.0% three times daily produced an average reduction of 3.3 mm Hg, and timolol twice daily an average reduction of 5.2 mm Hg.

Twice-daily dosing with brinzolamide 1.0% was clinically equivalent to three times daily dosing. The difference in mean intraocular pressure change from baseline between the two brinzolamide treatments was 0.5 mm Hg or less at all visits over the study period. These mean differences are smaller than normal variations observed between repeated intraocular pressure measurements (2 to 3 mm Hg) with Goldmann tonometry and therefore are not clinically relevant.[6–8] Twice-daily dosing with brinzolamide 1.0% was also statistically equivalent to three times daily dosing in reducing intraocular pressure from baseline at all visits. The upper 95% confidence limit for the difference in

TABLE 2. Distribution by Reason and Treatment Group of Patients Discontinued After Randomization

Reason Discontinued	Randomized Treatment Group: Brinzolamide 1% BID	Brinzolamide 1% TID	Timolol 0.5% BID	Total
Adverse event	21	17	8	46
Other*	4	19	6	39
Inadequate IOP control†	9	13	1	23
Patient decision‡	2	4	5	11
Lost to follow-up	5	7	4	16
Noncompliance with study medication or visit schedule	3	3	3	9
Totals	54	63	27	144

BID = two times daily; IOP = intraocular pressure; OH = ocular hypertension; POAG = primary open-angle glaucoma; TID = three times daily.

*The format was amended after the study was initiated to extend the treatment period from 12 to 18 months. Many patients (n = 27) decided to exit the study at month 12, and their decision was unrelated to study drug.

†P = .100 in chi-square test of independence comparing treatments for the percentage of patients who discontinued the study as treatment failure.

‡Unrelated to study medication (for example, relocation, intercurrent illness, and so forth).

TABLE 3. Analysis of Covariance for Per Protocol Data

Treatment	Baseline Means for Per Protocol Data: IOP mm Hg							
BID brinzolamide 1.0%				25.1				
TID brinzolamide 1.0%				26.1				
Timolol 0.5%				25.4				
P value				.0288				
Baseline analysis of variance								
Mean IOP Change From Baseline at Each Treatment Visit								
Treatment	Overall	1	3	6	9	12	15	18
Brinzolamide BID								
Mean change	−3.3	−3.5	−3.3	−3.9	−3.3	−3.2	−2.7	−3.3
N		140	138	130	124	126	107	107
Brinzolamide TID								
Mean change	−3.3	−3.6	−3.8	−3.5	−3.1	−3.4	−2.8	−3.2
N		138	128	128	121	121	103	105
Timolol 0.5% BID								
Mean change	−5.2	−5.6	−5.6	−5.3	−4.9	−5.2	−4.7	−5.3
N		73	68	67	63	61	52	53

BID = two times daily; IOP = intraocular pressure; OH = ocular hypertension; POAG = primary open-angle glaucoma; TID = three times daily.

Mean *P* value = .0001 for all groups at all visits, with least squares means from analysis of covariance.

intraocular pressure reduction between brinzolamide two and three times daily doses was 1.39 mm Hg or less at all visits over the study period. This was within the 1.5 mm Hg confidence limit.

In this study, timolol 0.5% twice daily was included as an active control to validate the study design and to provide a comparison to a commonly used and well-accepted therapeutic agent. Trough measurements showed mean changes from baseline for timolol 0.5% ranged from −4.7 to −5.6 mm Hg and were statistically significant at all visits ($P < .0001$). The intraocular pressure reductions with timolol 0.5% were consistent with expectations and were significantly greater than those with brinzolamide ($P < .0002$; Table 3).

Adverse events were defined as any clinically significant changes from baseline in a patient's ophthalmic and/or medical health that occurred during the course of the study and were obtained as solicited complaints or investigator observations. There were no serious adverse events related to any of the study medications. Adverse events related to

TABLE 4. Most Frequent Ocular and Nonocular Adverse Events

Event	Brinzolamide 1.0% BID, N = 150		Brinzolamide 1.0% TID, N = 153		Timolol 0.5% BID, N = 75	
Ocular	N	%	N	%	N	%
Blurred vision	12	8.0	8	5.2	4	5.3
Pain	6	4.0	1	0.7	2	2.7
Discomfort	5	3.3	9	5.9	6	8.0
Hyperemia	4	2.7	6	3.9	0	
Eye discharge	4	2.7	3	2.0	0	
Blepharitis	3	2.0	6	3.9	2	2.7
Keratitis	3	2.0	2	1.3	1	1.3
Foreign body	2	1.3	5	3.3	2	2.7
Sensation						
Dry eye	2	1.3	5	3.3	0	
Conjunctivitis	2	1.3	2	1.3	1	1.3
Lid margin	2	1.3	0		1	1.3
Crusting						
Nonocular						
Taste perversion	5	3.3	12	7.8	0	

BID = two times daily; TID = three times daily.

TABLE 5. Endothelial Cell Density (cells/mm^2) Change From Baseline

Treatment	Baseline	Month 6	Month 12	Month 18
Brinzolamide BID				
Mean	2528.2	165.7	57.5	4.7
STD	474.5	496.1	455.5	500.7
N	145	114	104	85
Brinzolamide TID				
Mean	2459.2	191.5	107.1	23.4
STD	474.3	544.5	472.8	496.8
N	146	111	99	84
Timolol BID				
Mean	2403.9	222.0	117.8	101.6
STD	480.7	564.9	490.9	595.2
N	74	62	55	47

BID = two times daily; OH = ocular hypertension; POAG = primary open-angle glaucoma; STD = standard deviation; TID = three times daily.

P = −.7976 from analysis of variance comparing treatment groups.

TABLE 6. Corneal Thickness (mm) Change From Baseline

Treatment	Baseline	Month 6	Month 12	Month 18
Brinzolamide BID				
Mean	0.5711	0.0044	0.0028	0.0015
STD	0.0420	0.0251	0.0278	0.0276
N	146	120	113	85
Brinzolamide TID				
Mean	0.5761	0.0010	0.0013	0.0056
STD	0.0447	0.0174	0.0249	0.0216
N	152	122	144	85
Timolol BID				
Mean	0.5719	0.0024	0.0003	−0.0009
STD	0.0508	0.0415	0.0380	0.0266
N	74	66	56	47

BID = two times daily; OH = ocular hypertension; POAG = primary open-angle glaucoma; STD = standard deviation; TID = three times daily.

P = .2152 from analysis of variance comparing treatment groups.

two and three times daily dosing with brinzolamide were nonserious, generally mild to moderate, and usually resolved without treatment. The most commonly occurring (at an incidence less than 4%) ocular adverse events related to all study medications were blurred vision and ocular discomfort. Ocular discomfort (that is, burning or stinging) related to timolol 0.5% occurred at a higher incidence (8.0%) than with brinzolamide 1.0% twice daily (3.3%) or brinzolamide 1.0% three times daily (5.9%; Table 4).

The ocular safety of brinzolamide was further demonstrated by the maintenance of patients' corneal health. Overall, no mean decrease in endothelial cell density was observed in any treatment group at the final visit and no statistically significant ($P = .7976$) difference in the mean change from baseline was observed between treatment groups (Table 5). In addition, no clinically relevant or statistically significant ($P = .2152$) difference in corneal thickness was observed between treatment groups over the 18-month study period, indicating no detrimental effect on corneal endothelial cell function (Table 6). There were also no clinically relevant changes in the other ocular safety parameters.

Brinzolamide was also found to be without significant systemic side effects. Mean total carbonic anhydrase activity over 18 months was 45% (two times daily) and 49% (three times daily) of baseline levels, and this inhibition is insufficient to produce clinically relevant systemic side effects (Table 7).[9]

This observation was supported by the lack of classic carbonic anhydrase inhibitor–related systemic side effects of oral usage.[9] There was no anecdotal evidence of systemic acidosis and limited reports of paresthesia, lethargy, and gastrointestinal-related side effects. There were no clinically relevant changes in hematology, blood chemistry, or urinalysis evaluations. The most common nonocular event related to therapy was taste perversion (Table 7).

TABLE 7. Mean Total CA and CA-II Activities in Red Blood Cells (% of Prestudy): Brinzolamide Treatment Groups

		Month					
		3	6	9	12	15	18
Group	Activity	% SD (N)	% SD (N)	% SD (N)	% SD (N)	% SD (N)	% SD (N)
BID	Total	58.1 ± 21.1 (26)	47.3 ± 17.4 (23)	46.6 ± 12.9 (21)	45.0 ± 12.9 (22)	45.1 ± 12.4 (17)	45.0 ± 12.1 (18)
	CA						
	CA-II	41.2 ± 29.1 (26)	25.5 ± 23.1 (23)	20.3 ± 17.0 (21)	21.1 ± 16.7 (22)	17.9 ± 15.4 (17)	18.3 ± 13.0 (18)
TID	Total	52.8 ± 20.1 (22)	46.5 ± 18.7 (21)	45.0 ± 16.1 (17)	45.5 ± 21.4 (19)	29.0 ± 21.7 (10)	49.1 ± 22.9 (12)
	CA						
	CA-II	28.3 ± 29.3 (22)	22.1 ± 26.4 (21)	19.6 ± 24.4 (17)	23.8 ± 33.0 (19)	20.2 ± 29.6 (10)	23.3 ± 33.0 (12)

BID = two times daily; CA = carbonic anhydrase; TID = three times daily.
Each value represents mean red blood cell activity ± SD. The number used for mean calculation is indicated in parentheses.

DISCUSSION

TOPICAL OCULAR DOSING TWO OR THREE TIMES DAILY with brinzolamide 1.0% ophthalmic suspension produced clinically relevant and statistically significant intraocular pressure changes from baseline in patients with primary open-angle glaucoma or ocular hypertension. The intraocular pressure reductions were maintained for the 18-month treatment period. The clinical and statistical equivalence of two and three times daily dosing with brinzolamide was demonstrated at all study visits. These findings support those from a previous study in which two and three times daily dosing with brinzolamide produced equivalent intraocular pressure reductions.[4]

The results from this study also show that brinzolamide 1.0% is safe and well tolerated when used for long-term therapy. Adverse events were nonserious and generally mild to moderate. Patients treated with timolol 0.5% reported ocular discomfort more frequently than those treated with two or three times daily brinzolamide 1.0%. This result is especially significant, because dorzolamide 2.0% has been shown to have a greater incidence of ocular discomfort than timolol 0.5% or brinzolamide 1.0%.[4,5] The difference in ocular discomfort is likely related to differences in pH and buffer capacity of the formulation. The pH of brinzolamide 1.0% is 7.5, and the pH of dorzolamide 2.0% is 5.6.

The safety of long-term treatment with brinzolamide 1.0% was also demonstrated by the lack of clinical or statistical differences from baseline in corneal health, ocular findings, and blood chemistry. In addition, CA inhibition was below the level known to cause side effects, thus demonstrating the systemic safety of topical brinzolamide.

Primary open-angle glaucoma is a disease that generally requires lifelong treatment. The most effective medications for long-term therapy are those that are efficacious, convenient, well tolerated, and show few if any side effects. This study demonstrated that the intraocular pressure-lowering efficacy of brinzolamide 1.0% twice daily is clinically relevant and statistically significant compared with baseline and that it is equivalent to three times daily dosing. In those patients for whom β blockers are contraindicated, brinzolamide offers an effective alternative that is well tolerated with less discomfort than timolol 0.5% and no evidence of the side effects usually associated with oral carbonic anhydrase inhibitors.

ACKNOWLEDGMENT

Statistical consultation was provided by Mark VonTress, PhD, and Russell Andrew, MS, Alcon Laboratories, Inc, Ft Worth, Texas.

THE BRINZOLAMIDE LONG-TERM THERAPY STUDY GROUP INVESTIGATORS

Delmar R. Caldwell, MD, Tulane University, New Orleans, Louisiana; John S. Cohen, MD, Cincinnati Eye Institute, Cincinnati, Ohio; George A. Cioffi, MD, Devers Eye Institute, Portland, Oregon; Miles A. Galin, MD, East Side Ophthalmology, New York, New York; Stephen C. Foster, MD, Boston, Massachusetts; Michael S. Kottler, MD, Rocky Mountain Eye Center, Salt Lake City, Utah; Wayne F. March, MD, University of Texas Medical Branch at Galveston, Galveston, Texas; John C. Morrison, MD, Casey Eye Institute, Portland, Oregon; Kenneth W. Olander, MD, Milwaukee, Wisconsin; Janis Reed, MD/Judie Charlton, MD (Dr Charlton replaced Dr Reed as principal investigator before study completion.), Morgantown, West Virginia; Michael Rotberg, MD, Charlotte Eye, Ear, Nose and Throat Association, Charlotte, North Carolina; Howard I. Schenker, MD, Rochester, New York; Elizabeth D. Sharpe, MD, Mount Pleasant, South Carolina; Doug H. Shin, MD, Kresge Eye Institute, Detroit, Michigan; Shannon L. Smith, MD, Nacogdoches, Texas; Jan H. Stahl, MD, Golden, Colorado; William C. Steward, MD, Charleston, South Carolina; Michael Stiles, MD, Hunkeler Eye Institute, Kansas City, Missouri.

REFERENCES

1. Maren TH. HCO_3 formation in aqueous humor: mechanism and relation to the treatment of glaucoma. Invest Ophthalmol Vis Sci 1974;13:479.
2. Maren TH. The rates of movements of Na^+Cl^- and HCO_3 from plasma to posterior chamber: effect of acetazolamide and relation to the treatment of glaucoma. Invest Ophthalmol 1983;28(suppl):280–284.
3. Stahlman E, Tipping R, Vogel R. A six-week dose-response study of the ocular hypotensive effect of dorzolamide with a one-year extension. Dorzolamide Dose-Response Study Group. Am J Ophthalmol 1996;122:183–194.
4. Silver L and the Brinzolamide Primary Therapy Study Group. Clinical efficacy and safety of brinzolamide (Azopt®), a new topical carbonic anhydrase inhibitor for primary open-angle glaucoma and ocular hypertension. Am J Ophthalmol 1998; 126:400–408.
5. Camras CB and the Brinzolamide Primary Therapy Study Group. A triple-masked, primary therapy study of the efficacy and safety of BID and TID dosed brinzolammide 1.0% compared to TID dosed dorzolamide 2.0% and BID dosed timolol 0.5%. Invest Ophthalmol Vis Sci 1997;38: S560.
6. Kass MA. Standardizing the measurement of intraocular pressure for clinical research guidelines from the Eye Care Technology Forum. Ophthalmology 1996;103:138–135.
7. Motoklo MA, Feldman F, Hyde M, Hurdy P. Sources of variability in the results of applanation tonometry. Can J Ophthalmol 1982;17:93–95.
8. Phelps CD, Phelps GK. Measurement in intraocular pressure: a study of its reproducibility. Graefes Arch Clin Exp Ophthalmol 1976;198:39–43.
9. Maren T. The relation between enzyme inhibition and physiological response in the carbonic anhydrase system. J Pharmacol Exp Ther 1963;139:140–153.