Clinical Efficacy and Safety of Brinzolamide (Azopt™), a New Topical Carbonic Anhydrase Inhibitor for Primary Open-angle Glaucoma and Ocular Hypertension

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• PURPOSE: To determine the intraocular pressure-lowering efficacy and safety of brinzolamide 1.0%, compared with dorzolamide 2.0% and timolol 0.5%.

• METHODS: A multicenter, double-masked, prospective, parallel-group study was conducted to compare brinzolamide 1.0%, administered two and three times a day, dorzolamide 2.0% three times a day, and timolol 0.5% twice a day in 572 patients with primary open-angle glaucoma or ocular hypertension. The primary end point was diurnally corrected intraocular pressure reduction from baseline, evaluated at both peak and trough times during a 3-month period.

• RESULTS: Mean intraocular pressure changes after twice daily (−3.8 to −5.7 mm Hg) and three times daily (−4.2 to −5.6 mm Hg) dosing with brinzolamide 1.0% were statistically equivalent (confidence limit ≤ 1.5 mm Hg) to each other and also to dorzolamide 2.0% three times a day (−4.3 to −5.9 mm Hg). The range of intraocular pressure change with timolol 0.5% twice daily was −5.2 to −6.3 mm Hg. Clinically relevant intraocular pressure changes (reduction ≥ 5 mm Hg or intraocular pressure ≤ 21 mm Hg) were observed in up to 75.7% of patients taking brinzolamide twice daily and in up to 80.1% taking brinzolamide three times daily. Treatment with brinzolamide 1.0% was safe, comfortable, and well tolerated. The incidence of ocular discomfort (burning and stinging) on instillation of brinzolamide (twice daily, 1.8%; three times daily, 3.0%) was significantly less (P = .000) compared with treatment with dorzolamide (16.4%).

• CONCLUSIONS: Brinzolamide 1.0% produced clinically relevant intraocular pressure reductions in substantial numbers of patients. Brinzolamide's effectiveness equaled that of dorzolamide 2.0% and it produced less ocular discomfort (burning and stinging) on instillation. (Am J Ophthalmol 1998;126:400–408. © 1998 by Elsevier Science Inc. All rights reserved.)

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BRINZOLAMIDE (AL-4862, AZOPT; ALCON LABORAtories Inc, Fort Worth, Texas) is a new topically active carbonic anhydrase inhibitor derived from a novel class of heterocyclic sulfonamides developed to be safe and comfortable and to lower and control elevated intraocular pressure (IOP). It has high affinity and inhibitory activity against human CA II, which is the key isoenzyme controlling aqueous humor production. Brinzolamide is formulated at physiologic pH as an aqueous suspension.[1,2] Dose-response studies comparing brinzolamide suspensions of 0.3%, 1.0%, 2.0%, and

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3.0% administered twice daily (bid) demonstrated that the 1.0% concentration was at the top of the IOP-lowering dose-response curve (Alcon Laboratories Inc, unpublished data, 1998). Other topically active carbonic anhydrase inhibitors, including dorzolamide (Trusopt; Merck & Co, Inc, West Point, Pennsylvania), demonstrated that a 2.0% concentration was generally most efficacious in reducing elevated IOP.[3]

Clinical studies to date of the comfort, safety, and efficacy of brinzolamide 1.0% ophthalmic suspension have demonstrated that it is well tolerated and does not cause many of the troublesome side effects associated with the use of oral carbonic anhydrase inhibitors.[4–6] Moreover, this brinzolamide suspension provides statistically significant IOP reductions from baseline that are clinically relevant in the majority of patients when used as primary or adjunctive therapy.[5,6] In this study, we compared the comfort, safety, and IOP-lowering efficacy of brinzolamide 1.0% (bid and three times daily [tid]) with dorzolamide 2.0% tid and timolol 0.5% bid in patients with primary open-angle glaucoma or ocular hypertension.

PATIENTS AND METHODS

THIS WAS A MULTICENTER (42 SITES), DOUBLE-masked, prospective, parallel-group, active-controlled trial. Patients enrolled were adults at least 21 years of age of any race and either sex diagnosed with primary open-angle glaucoma (with or without a pseudoexfoliation or pigment dispersion component) or ocular hypertension.

Excluded from this study were patients with only one sighted eye or amblyopia or best-corrected Snellen visual acuity worse than 20/80 in either eye; and those with a history of chronic or recurrent inflammatory eye disease, ocular trauma within the past 6 months, ocular infection within the past 3 months, corneal abnormality preventing reliable applanation tonometry, severe retinal disease or other severe ocular disease such as glaucomatous damage with a cup/disc ratio greater than 0.8, split fixation or clinically significant (in the investigator's opinion) field loss within the central 20 degrees, or legal blindness in either eye. Also excluded were patients who had intraocular surgery within the past 12 months, laser surgery within the past 3 months, history of hematologic disorders other than mild anemia, patients with severe, unstable, or uncontrolled cardiovascular or pulmonary disease that would preclude use of an ophthalmic beta-blocker, and those with any form of glaucoma other than primary open-angle glaucoma (with or without a pigment dispersion or pseudoexfoliation component). Women who were pregnant or nursing were also excluded. All women of childbearing potential were required to be using adequate birth control and were tested for pregnancy before entry into the study and on exiting from the study. Other patients excluded were those with an inability to discontinue contact lens wear during the study and those currently using any ophthalmic, dermatologic, or systemic corticosteroid, or having had therapy with an investigational agent within the past 30 days. Patients with a history of severe or serious hypersensitivity to oral or topical carbonic anhydrase inhibitors, sulfonamide drugs, or any components of these medications were excluded. In addition, patients with clinically significant hematologic, electrolyte, renal, or hepatic abnormalities based on laboratory testing at the first eligibility visit were also excluded. Finally, patients were excluded if they used any systemic medication that would affect IOP with less than a 1-month stable dosing regimen before the screening visit.

The study included a run-in phase (washout and eligibility) and a masked treatment phase. Patients were screened initially for adherence to the protocol inclusion/exclusion criteria; if they qualified, written informed consent was obtained. A screening visit (Snellen visual acuity, biomicroscopy, dilated fundus examination) was conducted, and qualifying patients then entered the run-in phase during which current ocular hypotensive medications were discontinued. There was a minimum washout period of 3 weeks for beta-blockers, 2 weeks for alpha-agonists and sympathomimetics, and 5 days for carbonic anhydrase inhibitors and miotics.

After the appropriate washout period, two eligibility examinations were conducted at a 1-week interval. The first eligibility visit included an ophthalmic examination consisting of Snellen visual acuity, biomicroscopy, and diurnal IOP measure-

ments using Goldmann applanation tonometry. Additional testing included hematology, blood chemistry, and urinalysis. Resting blood pressure and pulse were also recorded. Qualifying mean IOPs at this visit were 24 to 36 mm Hg, inclusive, in at least one eye at the 8 AM measurement time, and 21 to 36 mm Hg, inclusive, at 10 AM and 6 PM, with no greater than a 5-mm Hg difference between eyes at each time.

Patients who qualified returned for the second eligibility visit and followed the same procedure as for the first eligibility visit with the exception that automated perimetry (Humphrey program 24-2 or 30-2; Octopus program G1 or G1X) was performed and no laboratory specimens were collected. The same eyes were required to meet the IOP entry criteria (IOP range and symmetry) at all IOP measurements at both eligibility visits.

Patients who met all entry criteria were randomly assigned in a 2:2:2:1 ratio into four treatment groups as follows: brinzolamide 1.0% bid; brinzolamide 1.0% tid; dorzolamide 2.0% tid (Trusopt); and timolol 0.5% solution bid (Timoptic), respectively. All clinical supplies were labeled based on a computer-generated randomization code and dispensed in numerical sequence to patients at each investigational site. Patients were instructed to initially begin using the masked medication the morning after the second eligibility visit.

Masking for the bid and tid dosing regimens was maintained by providing each patient with three masked bottles labeled as "morning," "afternoon," and "nighttime," intended for instillation at 8 AM, 4 PM, and 10 PM, respectively. Patients on the tid regimen had either brinzolamide 1.0% or dorzolamide 2.0% in each bottle, while those taking bid brinzolamide or timolol had active medication in the "morning" and "nighttime" bottles and placebo in the "afternoon" bottle. Medication was instilled 15 to 30 minutes after the 8 AM IOP measurement by the study staff at each monthly office examination.

The treatment phase lasted for 3 months, during which time patients were seen at monthly intervals. At each visit, Snellen visual acuity, biomicroscopy, and resting pulse and blood pressure measurements were performed. The IOP was measured at 8 AM (10 hours after drug instillation the night before) and 10 AM (2 hours after drug instillation) at the 1-, 2-, and 3-month visits. In addition, IOP was also measured at 6 PM (2 and 10 hours after drug instillation for the tid and bid groups, respectively) at the 2- and 3-month visits. A dilated fundus examination and automated perimetry were performed at the 3-month visit in addition to hematology, blood chemistry, and urinalysis testing. Patients who were judged by the investigator to require additional ocular hypotensive therapy to control IOP, after randomization, were discontinued from the study.

The primary objective of this study was to compare the IOP-lowering efficacy of both dosage regimens of brinzolamide 1.0% to each other and also to that of dorzolamide 2.0%. Timolol 0.5% was included as a reference standard against which the IOP-lowering efficacy of brinzolamide and dorzolamide could be evaluated and for study validation purposes.

The primary efficacy end point was the diurnally corrected IOP change from baseline. The efficacy analysis was based on a per-protocol data set that included all evaluable patients and eyes that met the inclusion/exclusion criteria. If both eyes were considered evaluable, the IOP was the average of both eyes at baseline and all subsequent follow-up visits. If only one eye qualified, then IOP data only from that eye were used at baseline and all subsequent visits. Patients who discontinued treatment because of lack of IOP-lowering efficacy had their last IOP observation carried forward in the per-protocol analysis. The safety analysis was based on an intent-to-treat data set and included all patients who received study medication.

Sample size determinations were based on the ability to establish statistical equivalence between treatment groups using 95% confidence intervals. The power of the study, based on the sample size, to detect a statistical difference between the treatment groups was greater than 90%. Treatments were declared statistically equivalent if the two-sided 95% confidence interval of the difference in mean IOP change from baseline between treatments fell within $\pm$ 1.5 mm Hg. In addition, treatments were declared clinically equivalent if the difference in mean IOP change from baseline between treatments was $\leq$1.0 mm Hg. A repeated-measures analysis of variance model (Proc Mixed, SAS Version 6.10)

TABLE 1. Patient Demographics

	Treatment Group (No. [%])				
	Brinzolamide 1% bid	Brinzolamide 1% tid	Dorzolamide 2% tid	Timolol 0.5% bid	*P* Value*
Age (yrs)					
<65	78 (52.0)	77 (52.0)	72 (48.3)	36 (55.4)	.796
≥65	72 (48.0)	71 (48.0)	77 (51.7)	29 (44.6)	
Sex					
Male	66 (44.0)	78 (52.7)	65 (43.6)	30 (46.2)	.368
Female	84 (56.0)	70 (47.3)	84 (56.4)	35 (53.8)	
Race					
White	123 (82.0)	121 (81.8)	121 (81.2)	48 (73.8)	.493
Black	19 (12.7)	22 (14.9)	20 (13.4)	15 (23.1)	
Asian	0 (0)	1 (0.7)	0 (0)	0 (0)	
Other	8 (5.3)	4 (2.7)	8 (5.4)	2 (3.1)	
Iris color					
Brown	74 (49.3)	66 (44.6)	74 (49.7)	34 (52.3)	.342
Hazel	19 (12.7)	14 (9.5)	25 (16.8)	8 (12.3)	
Green	10 (6.7)	8 (5.4)	6 (4.0)	1 (1.5)	
Blue	43 (28.7)	50 (33.8)	41 (27.5)	18 (27.7)	
Gray	4 (2.7)	10 (6.8)	3 (2.0)	4 (6.2)	
Diagnosis					
OH	58 (38.7)	66 (44.6)	60 (40.3)	22 (33.8)	.754
POAG	90 (60.0)	82 (55.4)	86 (57.7)	42 (64.6)	
PD	1 (0.7)	0 (0)	2 (1.3)	1 (1.5)	
PE	1 (0.7)	0 (0)	1 (0.7)	0 (0)	

bid = twice daily; tid = three times daily; OH = ocular hypertension; POAG = primary open-angle glaucoma; PD = pigmentary dispersion glaucoma; PE = pseudoexfoliative glaucoma.

**P* values from chi-square test of independence.

was used and comparisons were based on treatment by time least-squares means. Fisher exact test was used to statistically compare the frequencies of adverse events.

RESULTS

A TOTAL OF 574 PATIENTS FROM 42 INVESTIGATIONAL sites were randomly assigned to treatment. A total of 572 patients received at least one dose of test medication and were thus included in the safety analyses. Two patients randomly assigned to treatment (one each taking dorzolamide 2.0% and timolol 0.5%) were discontinued from the study before they used the test medication because of personal reasons.

An additional 60 patients randomly assigned to treatment were not evaluable for efficacy and thus were excluded from the primary efficacy analyses. This included 15 patients taking brinzolamide bid, 21 patients taking brinzolamide tid, 16 patients taking dorzolamide, and 8 patients taking timolol. The reasons for exclusion included IOP asymmetry (n = 20), nonqualifying IOP (n = 16), contraindicated concomitant medication (n = 15), no on-therapy IOP data (n = 8), and inadequate washout (n = 1). This resulted in a total of 512 efficacy-evaluable patients.

A total of 40 patients were discontinued from the study after randomization. This included 10 patients taking brinzolamide bid, 16 patients taking brinzolamide tid, 10 patients taking dorzolamide, and 4 patients taking timolol. The reasons for discontinuation included an adverse event (n = 13), inadequate IOP control (n = 10), protocol violation (n = 9), patient decision (n = 5), lost to follow-up (n = 2), and noncompliance with study medication (n = 1).

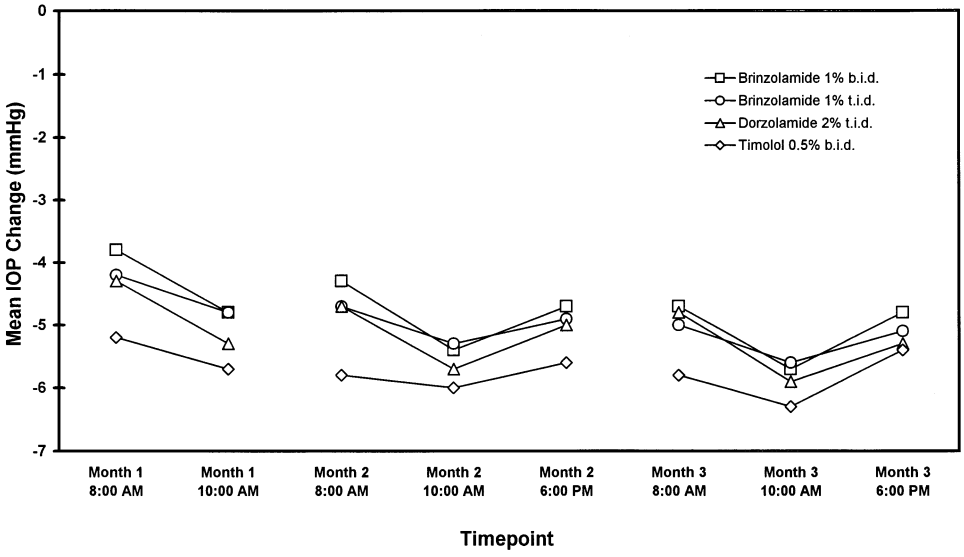

FIGURE. Mean change in IOP (mm Hg) for each treatment group by visit and time of day during the 3-month treatment period. Values reported are least-squares means (mm Hg) of the change from corresponding baseline diurnal IOP. All changes from baseline were statistically significant ($P = .0000$).

Patient demographics are compared in Table 1. No significant differences were observed between treatment groups with respect to age (elderly vs nonelderly) ($P = .796$), sex ($P = .368$), race ($P = .493$), iris color ($P = .342$), and ocular diagnosis ($P = .754$). In addition, there were no clinically or statistically ($P = .568$) significant differences between treatments with regard to the baseline IOP values at 8 AM, 10 AM, and 6 PM.

Treatment with brinzolamide 1.0% produced both clinically relevant and statistically significant ($P < .001$) IOP changes from baseline when administered either bid (−3.8 to −5.7 mm Hg) or tid (−4.2 to −5.6 mm Hg) at all times of day at all visits, as shown in the Figure. Changes in IOP from baseline after treatment with dorzolamide 2.0% tid (−4.3 to −5.9 mm Hg) and timolol 0.5% bid (−5.2 to −6.3 mm Hg) were also statistically significant ($P < .001$) at all visits. Mean IOP values by visit and time of day for all treatment groups are presented in Table 2.

The IOP-lowering efficacy of brinzolamide was further evaluated by an analysis of those patients who either responded (IOP reduction ≥ 5 mm Hg) or were considered to be controlled (IOP ≤ 21 mm Hg) (Table 3). The 5-mm Hg response criterion was based on the upper limit of the range of mean IOP reductions observed with brinzolamide in this study, and it represents an approximate 20% reduction from baseline in IOP. The 21-mm Hg IOP level criterion was selected as a target IOP often accepted for control in patients with elevated IOP. When analyzed in this fashion, the results with brinzolamide bid demonstrated that up to 75.7% of patients, depending on time of measurement, either responded or had their IOP controlled after treatment. Similarly, brinzolamide tid produced this level of response or control in up to 80.1% of patients, while dorzolamide did so in up to 80.0% of patients. Higher percentages of patients taking timolol (up to 90.2%) exhibited this level of response or control, as shown in Table 3.

Brinzolamide and dorzolamide were compared to assess both clinical (IOP difference ≤1.0 mm Hg) and statistical (upper 95% confidence limit ≤1.5 mm Hg) equivalence (Table 4). A comparison between brinzolamide tid and dorzolamide tid demonstrated a maximal mean IOP difference of 0.6 mm Hg across all visits during the 3-month treatment period. The upper 95% confidence limit was 1.24 mm Hg or less at all time points. Similarly, the brinzolamide bid vs dorzolamide tid maximal mean IOP difference was also 0.6 mm Hg or less across all visits, with an upper 95% confidence limit of 1.27

TABLE 2. Mean IOP by Visit and Time of Day

Treatment	Baseline			Month 1		Month 2			Month 3		
	8 AM	10 AM	6 PM	8 AM	10 AM	8 AM	10 AM	6 PM	8 AM	10 AM	6 PM
Brinzolamide											
1% bid											
Mean*	27.0	26.2	25.4	23.2	21.4	22.7	20.8	20.7	22.3	20.5	20.6
SD	2.4	2.7	2.8	3.3	3.2	3.2	3.0	3.1	3.7	3.4	3.0
N	150	150	150	150	149	145	144	143	145	144	142
Brinzolamide											
1% tid											
Mean	27.0	26.0	25.2	22.8	21.2	22.3	20.7	20.2	21.9	20.4	20.1
SD	2.6	2.7	2.7	3.3	3.1	3.3	3.4	3.0	3.3	3.2	3.0
N	148	148	148	148	148	142	142	139	141	140	136
Dorzolamide											
2% tid											
Mean	26.8	25.8	25.1	22.6	20.5	22.1	20.1	20.1	21.9	19.9	19.7
SD	2.4	2.5	2.8	3.6	3.1	3.8	3.4	3.3	3.6	3.1	3.2
N	149	149	149	148	148	145	145	142	146	146	145
Timolol											
0.5% bid											
Mean	26.5	25.9	25.2	21.4	20.2	20.6	19.8	19.5	20.7	19.5	19.7
SD	2.3	2.8	2.7	3.3	3.4	3.4	3.3	2.7	3.7	3.7	3.8
N	65	65	65	65	65	61	62	61	61	61	60

IOP = intraocular pressure; bid = twice daily; tid = three times daily.
*In mm Hg.

TABLE 3. Responder Analysis by Visit and Time of Day*

Treatment	% of Patients							
	Month 1		Month 2			Month 3		
	8 AM	10 AM	8 AM	10 AM	6 PM	8 AM	10 AM	6 PM
Brinzolamide 1% bid	42.7	69.1	51.7	74.3	70.6	53.8	75.7	72.5
Brinzolamide 1% tid	48.0	67.6	54.2	73.2	77.7	60.3	77.9	80.1
Dorzolamide 2% tid	45.3	65.5	52.4	72.4	74.6	55.5	78.1	80.0
Timolol 0.5% bid	63.1	67.7	68.9	77.4	90.2	73.8	82.0	76.7

IOP = intraocular pressure; bid = twice daily; tid = three times daily.
*Based on an analysis of patients who either responded (IOP reduction ≥5 mm Hg from baseline) or were controlled (IOP ≤21 mm Hg). The N values at each time point are identical to those in Table 2.

mm Hg or less at all time points. Finally, the brinzolamide bid vs brinzolamide tid maximal mean IOP difference was 0.4 mm Hg or less across all visits, with an upper 95% confidence limit of 1.09 mm Hg or less at all time points. These IOP differences and confidence limits are all within the range to establish both clinical and statistical equivalence between brinzolamide bid and tid and between brinzolamide (bid and tid) and dorzolamide.

Adverse events related to brinzolamide treatment generally occurred on instillation, were usually mild and nonserious, resolved without treatment, and generally did not interrupt continuation in the study. No serious events related to brinzolamide were reported and no patient was discontinued from the study because of a serious treatment-related event.

The most frequent adverse events reported at an incidence of 3% or greater in any treatment group

TABLE 4. Comparison of Mean IOP Changes and Confidence Intervals by Visit and Time of Day

	Month 1		Month 2			Month 3		
	8 AM	10 AM	8 AM	10 AM	6 PM	8 AM	10 AM	6 PM
Treatment								
Brinzolamide 1% bid	−3.8*	−4.8	−4.3	−5.4	−4.7	−4.7	−5.7	−4.8
Brinzolamide 1% tid	−4.2	−4.8	−4.7	−5.3	−4.9	−5.0	−5.6	−5.1
Dorzolamide 2% tid	−4.3	−5.3	−4.7	−5.7	−5.0	−4.8	−5.9	−5.3
Brinzolamide tid minus dorzolamide tid								
mm Hg	0.1	0.6	0.0	0.4	0.1	−0.2	0.3	0.3
Upper 95% CL	0.79	1.24	0.69	1.07	0.80	0.49	1.04	0.99
Lower 95% CL	−0.60	−0.14	−0.72	−0.34	−0.61	−0.91	−0.37	−0.42
Brinzolamide bid minus dorzolamide tid								
mm Hg	0.5	0.5	0.4	0.3	0.3	0.1	0.3	0.6
Upper 95% CL	1.16	1.17	1.08	0.96	1.03	0.77	0.95	1.27
Lower 95% CL	−0.22	−0.21	−0.32	−0.44	−0.37	−0.63	−0.45	−0.13
Brinzolamide bid minus brinzolamide tid								
mm Hg	0.4	−0.1	0.4	−0.1	0.2	0.3	−0.1	0.3
Upper 95% CL	1.07	0.62	1.09	0.60	0.94	0.98	0.62	1.00
Lower 95% CL	−0.32	−0.76	−0.31	−0.81	−0.47	−0.42	−0.78	−0.42

IOP = intraocular pressure; bid = twice daily; tid = three times daily; CL = confidence limit.
*All IOP changes are least-squares means (in mm Hg) from corresponding diurnal baseline.

TABLE 5. Most Frequent Adverse Events*

	No. (%)			
	Brinzolamide 1% bid (n = 165)	Brinzolamide 1% tid (n = 169)	Dorzolamide 2% tid (n = 165)	Timolol 0.5% bid (n = 73)
Ocular				
Blurred vision	5 (3.0)	6 (3.6)	1 (0.6)	0 (0)
Discomfort	3 (1.8)	5 (3.0)	27 (16.4)	2 (2.7)
Conjunctivitis	0 (0)	0 (0)	5 (3.0)	1 (1.4)
Nonocular				
Taste abnormality	5 (3.0)	13 (7.7)	7 (4.2)	0 (0)

*Table combines treatment-related and nonrelated adverse events and includes those that occurred at an incidence of 3% or greater in any treatment group.

included transient blurred vision, ocular discomfort (burning and stinging), conjunctivitis, and taste abnormality (Table 5). The incidence of ocular discomfort (burning and stinging) on instillation of either concentration of brinzolamide (bid, 1.8%; tid, 3.0%) was significantly less ($P = .0000$) compared with treatment with dorzolamide (16.4%). Other treatment-related ocular events that occurred at an incidence greater than 1% included foreign body sensation (tid brinzolamide, 1.8%), pruritus (tid brinzolamide, 1.2%; dorzolamide, 2.4%), tearing (tid brinzolamide, 1.2%; dorzolamide, 1.2%), and dry eye (tid brinzolamide, 1.2%).

No clinically significant difference in worsening from baseline of visual acuity, ocular signs, dilated fundus parameters, visual fields, pulse, or blood

pressure was observed among treatment groups. In addition, no clinically significant change in laboratory values for hematology, blood chemistry, or urinalysis variables was observed to occur either within or between all treatment groups.

DISCUSSION

THE IOP-LOWERING EFFICACY OF BRINZOLAMIDE (BID and tid) was demonstrated by both clinically relevant and statistically significant IOP reductions at similar peak (10 AM, 2 hours after dose) and trough (8 AM, 10 hours after dose) times during the dosing interval. In addition, the IOP-lowering efficacy of brinzolamide bid was further substantiated by IOP reductions at the 6 PM time point (10 hours after dose) that were very similar to those obtained with brinzolamide tid and dorzolamide tid at this time.

The results of this study also demonstrated that the IOP reductions after bid and tid dosing with brinzolamide 1.0% were both clinically (IOP difference ≤1.0 mm Hg) and statistically (upper 95% confidence limit ≤1.5 mm Hg) equivalent to each other and also to dorzolamide 2.0% tid. There was no loss of efficacy during the 3-month treatment period with either brinzolamide or dorzolamide. Comparisons between the brinzolamide (bid and tid) and dorzolamide treatment groups demonstrated IOP differences of ≤0.6 mm Hg and upper 95% confidence limits of ≤1.27 mm Hg at all time points during the 3-month treatment period.

Overall, fewer patients experienced an adverse event, either ocular or nonocular, in the brinzolamide bid group then in the brinzolamide tid and dorzolamide groups, which were similar. The numbers of patients discontinued from treatment for treatment-related or unrelated adverse events were five each for brinzolamide tid and dorzolamide tid and three for brinzolamide bid. There were no clinically relevant effects of brinzolamide (bid or tid) on visual acuity, biomicroscopic measures (eyelids, conjunctiva, iris, anterior chamber, lens, vitreous), ophthalmoscopic variables (retina, macula, choroid, optic nerve, disc pallor, cup/disc ratio), and visual fields. Blood chemistry, hematology, and urinalysis changes with brinzolamide were not clinically significant. No clinically significant effect on pulse and blood pressure occurred with brinzolamide. The side effects usually associated with orally administered carbonic anhydrase inhibitors were not observed with the topically administered agents used in this study.

Based on the relatively low incidence of side effects in clinical trials reported to date, topical carbonic anhydrase inhibitors fulfill the promise of circumventing many of the troublesome side effects produced by oral carbonic anhydrase inhibitors.[7,8] Topical carbonic anhydrase inhibitors offer distinct advantages over miotics and alpha-agonists as they are free of effects on the pupil and accommodation and have almost no central nervous system side effects. In addition, they should pose fewer problems than beta-blockers for patients with compromised cardiac or pulmonary function.

Dorzolamide, the first marketed topical carbonic anhydrase inhibitor, has a relatively high incidence of ocular discomfort on instillation.[3,9] Brinzolamide has been shown to produce less ocular discomfort (burning or stinging) on instillation than dorzolamide in the current study and in two additional comfort studies.[4] Since poor patient compliance with long-term glaucoma medical therapy has always been an issue of concern, it is conceivable that compliance would be improved with a therapy that produces little or no ocular burning and stinging.

Both brinzolamide and dorzolamide have the same efficacy for lowering elevated IOP.[5] The results of this study also indicate that brinzolamide bid produced a clinically significant lowering of IOP in a large percentage of patients. A dosage regimen of bid compared with tid may further improve patient compliance.

In summary, these results demonstrated that brinzolamide 1.0% ophthalmic suspension was safe and effective in reducing IOP in patients with glaucoma or ocular hypertension and was equivalent in efficacy to dorzolamide 2.0% ophthalmic solution while being more comfortable. Topical carbonic anhydrase inhibitors are a valuable new addition to the glaucoma medical armamentarium.

THE BRINZOLAMIDE PRIMARY THERAPY STUDY GROUP

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