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Adjunctive Therapy With Brinzolamide 1% Ophthalmic Suspension (Azopt®) in Patients With Open-Angle Glaucoma or Ocular Hypertension Maintained on Timolol Therapy

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Abstract. This prospective, multicenter, double-masked, placebo-controlled study evaluated the safety and efficacy of brinzolamide 1% ophthalmic suspension (Azopt®) when used adjunctively with open-label timolol maleate 0.5% (Timoptic®). One-hundred-thirty-two patients requiring an adjunctive therapy to timolol 0.5% for the treatment of open-angle glaucoma or ocular hypertension were randomized to receive brinzolamide or placebo three times daily (t.i.d.) in addition to timolol 0.5% twice daily (b.i.d.) for 3 months. Qualifying intraocular pressure (IOP) on timolol 0.5% b.i.d. was 24–36 mm Hg in at least one eye at 8:00 A.M. and 21–36 mm Hg at 10:00 A.M., with no greater than a 5–mm Hg difference between eyes, during two eligibility visits separated by at least 7 days. Treatments were compared using a repeated-measures analysis of variance. Adjunctive therapy with brinzolamide resulted in clinically and statistically significant reductions in IOP from the timolol baseline at all visits. IOP changes from a diurnal baseline ranged from −3.3 mm Hg to −4.1 mm Hg for brinzolamide (N = 53) compared with −0.9 mm Hg to −2.5 mm Hg for placebo (N = 55). Abnormal taste (7.7%) and transient blurred vision (6.2%) were the most frequently reported adverse events. No clinically significant differences in the incidence or severity of ocular signs, visual acuity, cup/disk ratio, or parameters studied on dilated fundus examination were observed between treatment groups. Brinzolamide 1% t.i.d., used adjunctively with timolol 0.5% b.i.d., is safe and well tolerated, and produces clinically and statistically significant additional IOP reductions. (**Surv Ophthalmol 44 [Suppl 2]**:S163–S168, 2000.

Key words. Azopt® • adjunctive therapy • brinzolamide • ocular hypertension • open-angle glaucoma • timolol

Therapy for glaucoma is individualized for each patient, with consideration of several factors, including intraocular pressure (IOP) and degree of optic nerve damage. Topical beta-adrenergic blocking agents have become the most common therapeutic agents used in the treatment of elevated IOP. However, treatment with a beta-adrenergic blocking agent alone is often insufficient to maintain a desirable IOP over the long term in many patients. Some patients have inadequate lowering of IOP, whereas others experience a "drift" back toward pretreatment levels. In all situations, a second agent that further lowers IOP may be required for additional control. Drugs such as cholinergics, sympathomimetics, alpha-agonists and prostaglandins have been added to the initial beta-blocker regimen with clinical success.

In the past, orally administered carbonic anhydrase inhibitors (CAIs) have been added to timolol for patients with inadequate lowering of IOP. However, many patients are unable to tolerate oral CAIs because of systemic adverse effects, including paresthesias, tinnitus, nausea, anorexia, and gastrointestinal disturbances. These symptoms occur with even greater frequency and severity in the elderly, a common population of glaucoma patients.[2] Recently, topical CAIs have been developed with the advantage that a much lower dose applied directly to the eye is associated with a very low incidence of systemic side effects.

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The results of previous controlled clinical studies have established the safety and IOP-lowering efficacy of topically formulated brinzolamide in patients with open-angle glaucoma or ocular hypertension.[1,3–6] This prospective, multicenter, double-masked, parallel-group, placebo-controlled study was designed to evaluate the safety and additive efficacy of brinzolamide 1% ophthalmic suspension administered three times daily (t.i.d.) when used adjunctively with timolol maleate 0.5% administered twice daily (b.i.d.) in patients with open-angle glaucoma or ocular hypertension. The results of this study have been published previously in abstract form.[5]

Methods

Patients of any race and either sex were enrolled if they were at least 21 years of age and had been diagnosed with primary open-angle glaucoma, open-angle glaucoma, pseudoexfoliative or pigmentary glaucoma, or ocular hypertension. Primary open-angle glaucoma was defined as elevated IOP with clinically relevant visual field loss and anatomic changes in the optic nerve head, and ocular hypertension was defined as elevated IOP without clinically relevant visual field loss and optic nerve head changes.

Patients with a history of ocular trauma or infection, severe retinal disease, ocular pathology, hematologic disorders other than mild anemia, intraocular surgery within the past 12 months, laser surgery within the past 3 months, or therapy with another investigational agent within the past 30 days were excluded from the study. Also excluded were those who were pregnant or nursing and those with any of the following: only one sighted eye, amblyopia, or best-corrected visual acuity worse than 20/80 in either eye; chronic inflammatory ocular disease; any abnormality preventing reliable applanation tonometry; hypersensitivity to oral or topical CAIs, sulfonamide drugs, or any components of these medications; long-term use of any systemic medication that could affect IOP with less than a 1-month stable dosing regimen; severe, unstable, or uncontrolled cardiovascular or pulmonary disease; clinically significant hematologic, electrolyte, renal, or hepatic abnormalities; current use of any corticosteroid; any form of glaucoma other than those specified in the inclusion criteria; and inability to discontinue contact lens wear during the study. This study was approved by an institutional review board before initiation. Patients meeting the screening criteria signed an institutional review board–approved informed consent document.

Medical history and demographic information were recorded, and enrolled patients underwent an ophthalmic evaluation that included best-corrected Snellen visual acuity, biomicroscopy, dilated fundus examination, optic nerve head evaluation (cup/disk), and gonioscopy. Resting blood pressure and heart rate were measured. A negative urine pregnancy test was required of all women of childbearing potential. During the 4-week eligibility phase, all patients received open-label treatment with timolol 0.5% administered topically at 8:00 A.M. and 10:00 P.M. Any concomitant ocular hypotensive medication(s) were discontinued at the screening visit when the open-label timolol was initiated. Patients then returned for two examinations, scheduled 1 week apart, to establish eligibility for the treatment phase. At each of these examinations, patients underwent best-corrected Snellen visual acuity, biomicroscopic examination, IOP measurements with Goldmann applanation tonometry, and blood pressure and resting heart rate measurements at 8:00 A.M. (before timolol instillation) and again at 10:00 A.M. (approximately 2 hours after instillation of the morning dose of timolol). IOP was measured twice on any one eye, and if the measurements differed by more than 4 mm Hg, a third IOP measurement was taken. The IOP measurements closest to each other were then averaged. At each eligibility examination, only those patients with an 8:00 A.M. IOP of 24 to 36 mm Hg and a 10:00 A.M. IOP of 21 to 36 mm Hg, inclusive, in at least one eye (the same eye) and an IOP difference of no greater than 5 mm Hg between eyes were qualified to continue. If both eyes qualified for the study, the IOPs of both eyes were averaged and reported. In addition to the above procedures, a complete blood cell count, blood chemistry, and urinalysis were performed during the first eligibility examination, and automated perimetry (using either a Humphrey or an Octopus automated perimeter) was performed after the 10:00 A.M. measurements during the second eligibility examination.

Qualifying patients entered the double-masked treatment phase and were randomly assigned in equal ratios to receive brinzolamide 1% ophthalmic suspension t.i.d. or placebo t.i.d., in addition to open-label treatment with timolol b.i.d. Computer-generated randomization was used with codes assigned in numerical sequence. Test medications were supplied in masked 5-mL opaque dropper bottles. Patients instilled one drop of study medication into each eye t.i.d. at 8:00 A.M., 4:00 P.M., and 10:00 P.M. except on the days when they returned for examination, at which time medication was administered by the study staff. Timolol 0.5% was given 5–10 minutes before the 8:00 A.M. and 10:00 P.M. doses of study medication.

Patients returned at monthly intervals for 3 months. Examinations began at 8:00 A.M., before the morning dose of timolol 0.5% and masked study medication. At that time, the date and time of the

last timolol and study medication use was documented, resting pulse and blood pressure were measured, and an ophthalmic examination consisting of best-corrected Snellen visual acuity, slit-lamp examination, and IOP measurements were performed. IOP measurements were all performed with a Goldmann applanation tonometer, which was calibrated for accuracy a maximum of 2 months before initiation of the study, and the use of benoxinate hydrochloride/fluorescein sodium (Fluress). IOP measurements were taken by two individuals, an operator and a reader, and all IOP measurements for an individual patient were performed by the same operator using the same tonometer. If more than one operator performed IOP measurements on the same patient, the operator must have gone through a validation procedure indicating correct use of the tonometer. Approximately 15–30 minutes after the IOP assessment, the morning dose of timolol was instilled, and 5–10 minutes later, the morning dose of masked medication was instilled. The IOP was measured again at least 2 hours and no longer than 2.5 hours after the test drug was administered. At the month 3 examination, automated perimetry, urine pregnancy test for women of childbearing potential, blood and urine laboratory testing, and a dilated fundus examination were performed.

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.

Statistical analyses were performed on safety data from all patients who received study medication. Statistical analyses of efficacy were performed on data from the subset of those patients who met all of the entry criteria and were not entered in violation of the protocol (per-protocol dataset). The key efficacy analysis was based on the mean IOP change in millimeters of mercury from diurnal baseline comparing brinzolamide and placebo, with the use of a repeated-measures analysis of variance. Parametric analysis was used because assumptions of parametric analysis were met. Nonparametric analysis was not used because it does not adequately address repeated measures. All analyses were performed using SAS Version 6.10 for Windows.

Results

PATIENT POPULATION

One-hundred-thirty-two patients from 19 sites were randomized to treatment, received at least one dose of study medication, and were evaluated for

TABLE 1

Demographic Characteristics of Patients Evaluated for Efficacy

Characteristic	Brinzolamide 1% (N = 53)	Placebo (N = 55)	P Value*
Age (yrs)			
Mean ± SD	60.9 ± 13.0	62.6 ± 12.1	0.4749†
<65 (no. [%])	30 (56.6)	28 (50.9)	0.553‡
≥65 (no. [%])	23 (43.4)	27 (49.1)	
Sex (no. [%])			
Male	28 (52.8)	22 (40.0)	0.181
Female	25 (47.2)	33 (60.0)	
Race (no. [%])			
White	31 (58.5)	36 (65.5)	0.485
Black	15 (28.3)	15 (27.3)	
Asian	2 (3.8)	0 (0)	
Other	5 (9.4)	4 (7.3)	
Iris color (no. [%])			
Brown	32 (60.4)	30 (54.5)	0.597
Hazel	4 (7.5)	2 (3.6)	
Green	1 (1.9)	4 (7.3)	
Blue	15 (28.3)	18 (32.7)	
Gray	1 (1.9)	1 (1.8)	
Diagnosis (no. [%])			
Ocular hypertension	22 (41.5)	12 (21.8)	0.043
Open-angle glaucoma	31 (58.5)	41 (74.5)	
Pigment dispersion	0 (0)	2 (3.6)	

* χ^2 test of independence, except for comparison of mean age, which was analyzed by one-way analysis of variance.

† P value indicates no difference in mean values between the two groups (treatments).

‡ P values here and for remainder of Table 1 indicate no difference in relative proportion between subgroups for the two groups.

TABLE 2

Distribution by Reason and Treatment of Patients Discontinued After Randomization

Reason	Randomized Treatment Group (no.)		
	Brinzolamide 1% t.i.d.	Placebo	Total
Protocol violation	4	2	6
Inadequate IOP control	0	5	5
Adverse event	1	4	5
Lost to follow-up	0	2	2
Noncompliance with study medication	1	0	1
Patient relocation	0	1	1
Total	6	14	20

safety. Of these, 108 were included in the per-protocol efficacy analyses. The baseline demographic characteristics according to treatment group are presented in Table 1. There were no significant differences between treatment groups with respect to mean age, age distribution, sex, iris color, or race, indicating that these factors did not contribute to the response to the drug. The distribution by reason and treatment group of patients discontinued from this study after randomization is listed in Table 2; the most common reason was violation of the protocol. There were slightly more patients in the placebo group with primary open-angle glaucoma (74.5% vs. 58.5% in the brinzolamide group) and fewer with ocular hypertension (21.8% vs. 41.5%, respectively; $P = 0.043$ for the comparison). However, the IOP reductions were similar between treatment groups within each ocular diagnosis.

EFFICACY

Adjunctive treatment with brinzolamide 1% t.i.d. in patients receiving timolol 0.5% b.i.d. resulted in clinically and statistically significant reductions in IOP, compared with baseline and placebo treatment. As shown in Table 3, mean IOP changes from baseline ranged from −3.3 mm Hg to −4.1 mm Hg in the brinzolamide group compared with −0.9 mm Hg to −2.5 mm Hg in the placebo group. Changes from baseline were statistically significant ($P < 0.001$) for both groups at all visits. The IOP reductions in the brinzolamide group were significantly ($P \leq 0.0329$) greater at all visit times as compared to placebo.

SAFETY

The ocular safety profile of brinzolamide was evaluated in all 132 patients who participated in the study. Overall, brinzolamide was safe and well tolerated. Adverse events were infrequent, nonserious, and mild to moderate, and usually resolved without treatment.

As is shown in Table 4, the most frequent ocular adverse event in the brinzolamide treatment group was transient blurred vision (6.2%). The most frequent ocular adverse events in the placebo group were hyperemia (6.0%), pruritus (6.0%), discomfort (4.5%), and keratitis (4.5%). None of these symptoms was reported by any patient in the brinzolamide group. Abnormal taste (7.7%) was the most frequently reported nonocular event in the brinzolamide group.

No clinically or statistically significant differences in the incidence or severity of ocular signs, visual acuity, pulse, or blood pressure were observed between the treatment groups.

TABLE 3

*Mean IOP and IOP Changes From Baseline by Visit and Time of Day **

	Month 1		Month 2		Month 3	
	8 A.M.	10 A.M.	8 A.M.	10 A.M.	8 A.M.	10 A.M.
			Brinzolamide 1% t.i.d.			
N	52	52	53	53	51	51
Mean IOP (mm Hg)	22.2	20.8	21.8	20.4	21.3	20.8
Mean change (mm Hg)	−3.3†‡	−3.3†‡	−3.7†‡	−3.8†‡	−4.1†‡	−3.3†‡
% change	−13.2	−14.3	−14.9	−16.0	−16.6	−14.0
			Placebo			
N	55	55	49	49	49	49
Mean IOP (mm Hg)	23.6	23.0	23.1	22.6	23.1	23.1
Mean change (mm Hg)	−2.1†	−1.1†	−2.5†	−1.5†	−2.5†	−0.9†
% change	−8.4	−5.0	−10.3	−6.4	−10.4	−4.4

* Baseline IOP values at 8 A.M. and 10 A.M. were 25.5 and 24.2 mm Hg (brinzolamide) and 25.8 and 24.1 mm Hg (placebo).

† Statistically significant difference from baseline ($P < 0.001$).

‡ Statistically significant difference from placebo ($P \leq 0.033$).

IOP = intraocular pressure.

TABLE 4

*Frequency and Incidence of Most Prevalent Ocular and Nonocular Adverse Events **

Adverse Event	No. (%) Brinzolamide 1% (N = 65)	No. (%) Placebo (N = 67)
Ocular		
Blurred vision	4 (6.2)	1 (1.5)
Keratitis	2 (3.1)	3 (4.5)
Decreased vision	1 (1.5)	1 (1.5)
Hyperemia	0 (0)	4 (6.0)
Pruritus	0 (0)	4 (6.0)
Discomfort	0 (0)	3 (4.5)
Ocular pain	0 (0)	2 (3.0)
Abnormal vision	0 (0)	2 (3.0)
Lid edema	0 (0)	1 (1.5)
Nonocular		
Abnormal taste	5 (7.7)	0 (0)
Headache	3 (4.6)	1 (1.5)
Diarrhea	2 (3.1)	0 (0)
Increased cough	2 (3.1)	1 (1.5)
Sinusitis	2 (3.1)	1 (1.5)
Pharyngitis	1 (1.5)	1 (1.5)

* Incidence includes both related and nonrelated events. Patients in both treatment groups also received timolol 0.5% b.i.d.

Discussion

In patients receiving timolol 0.5% b.i.d. for the treatment of primary open-angle glaucoma or ocular hypertension, the addition of brinzolamide 1% t.i.d. resulted in clinically and statistically significant additional reductions in IOP from baseline. The observed IOP reductions were significantly greater than those observed in patients treated with timolol plus placebo.

These findings indicate that patients who do not respond adequately to single-drug treatment with topically administered timolol may benefit from the addition of brinzolamide 1% ophthalmic suspension t.i.d. to the treatment regimen. The reductions in IOP associated with the addition of brinzolamide in this study (−3.3 mm Hg to −4.1 mm Hg) were similar to those reported in timolol-treated patients who were treated adjunctively with dorzolamide 2% (−3.0 mm Hg to −3.7 mm Hg).[8]

Treatment with brinzolamide 1% was safe and well tolerated, which is not surprising in that brinzolamide 1% ophthalmic suspension, formulated at a physiologic pH of 7.5, is not likely to cause ocular discomfort. In fact, none of the patients in this study reported ocular discomfort (burning or stinging) when brinzolamide was given concomitantly with timolol. These results corroborate the findings of a previous study that evaluated ocular comfort associated with brinzolamide administration.[7]

The good tolerability and comfort of brinzolamide 1% ophthalmic suspension, in conjunction with its efficacy in lowering IOP, make it an excellent choice for adjunctive therapy in patients with primary open-angle glaucoma or ocular hypertension who are not responding adequately to timolol therapy alone. The combined use of brinzolamide and timolol results in clinically and statistically significant further reductions in IOP.

Addendum

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