Efficacy of brinzolamide and levobetaxolol in pediatric glaucomas: A randomized clinical trial

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PURPOSE To describe the safety and clinical response on elevated intraocular pressure (IOP) of brinzolamide and levobetaxolol in pediatric patients under 6 years of age.

METHODS A double-masked, randomized design. Pediatric patients were randomized to brinzolamide suspension, 1%, or levobetaxolol suspension, 0.5%, both dosed twice daily. IOPs at 9 AM were taken at screening, baseline, and weeks 2, 6, and 12. A descriptive study with mean change from baseline IOP, the primary efficacy parameter.

RESULTS Seventy-eight evaluable patients (32 brinzolamide and 46 levobetaxolol). Patients on no prestudy IOP-lowering therapy randomized to brinzolamide had mean IOP change from baseline ranging from −4.1 mm Hg (week 2) to −5.0 mm Hg (week 6). When all brinzolamide patients are considered, there was little mean change from baseline IOP due to the large number of patients enrolled without a washout of prior IOP-lowering therapy. Levobetaxolol patients had mean change from baseline, ranging from −1.8 mm Hg (week 6) to −2.9 mm Hg (week 2). Levobetaxolol patients on no prestudy therapy had mean IOP change from baseline ranging from −2.9 mm Hg (week 12) to −4.0 mm Hg (week 2). Brinzolamide was more efficacious for glaucoma associated with systemic or ocular abnormalities and less efficacious for primary congenital glaucoma. Levobetaxolol was most efficacious for primary congenital glaucoma. Adverse events were predominantly nonserious and did not interrupt patient continuation in the study.

CONCLUSIONS Both brinzolamide and levobetaxolol were well tolerated. Both drugs provided clinically relevant IOP reductions for patients not on a previous medication, although efficacy is, in part, contingent upon diagnosis. (J AAPOS 2008;12:239-246)

Glaucoma in children can result from a large variety of mechanisms, broadly divided into three categories: primary genetically determined glaucoma, glaucoma associated with systemic or ocular abnormalities, and secondary glaucomas.[1-3]

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Although intraocular pressure (IOP)-lowering medications, including prostaglandin analogues,[4,5] miotics,[3] carbonic anhydrase inhibitors,[3,6,7] and beta-adrenergic antagonists,[8-10] are used to treat glaucoma in children, the results of randomized, controlled, clinical evaluations of these compounds in children are only recently being published.[11]

Brinzolamide, a thienothiazine sulfonamide, is a potent inhibitor of carbonic anhydrase II.[12] The comfort, safety profile, and IOP-lowering effectiveness of brinzolamide ophthalmic suspension, 1% (marketed under the trade name AZOPT®, Alcon Laboratories, Fort Worth, TX), have been evaluated in over 20 clinical trials during which over 1700 adult subjects with open-angle glaucoma or ocular hypertension were exposed to the drug.[13-16]

Levobetaxolol (trade name BETAXON Alcon Laboratories, Fort Worth, TX™) is the (S)-isomer of betaxolol and is the more potent enantiomer with respect to activity at the β-adrenoreceptor,[17] consistent with the known stereo-selectivity of the βadrenoreceptor for this drug class. Levobetaxolol is a cardioselective adrenoreceptor antagonist.[17] Levobetaxolol was approved by the FDA in 2000 for the treatment of elevated IOP in adult patients with open-angle glaucoma or ocular hypertension.

Table 1. Patient enrollment age stratification

	Treatment					
	Brinzolamide		Levobetaxolol		Total	
Age group	Planned*	Actual	Planned*	Actual	Planned*	Actual
1 week to <1 year	5	6	5	9	10	16
1 year to <2 years	5	5	5	10	10	15
2 years to <4 years	10	10	10	17	20	27
4 years to <6 years	10	11	10	12	20	23
Total	30	32	30	48	60	80

*The FDA Written Requests for these drugs specified 30 patients per drug, allocated to each of four age strata as shown. Enrollment was continued until *all* age strata/treatment group subgroups met the FDA required number, resulting in over-enrollment for many of the subgroups (see Results).

Both brinzolamide and levobetaxolol are approved in the United States for the reduction of elevated IOP in adult patients with open-angle glaucoma or ocular hypertension; however, clinical investigations of the safety and efficacy of brinzolamide and levobetaxolol have not included prospective studies in children. The purpose of this descriptive study was to assess the safety and efficacy of brinzolamide and levobetaxolol for pediatric patients.

Subjects and Methods

This study was conducted at 25 sites throughout the United States (20 sites) and India (5 sites) in accordance with the Declaration of Helsinki. This double-masked, randomized, parallel group study was designed to describe the safety and IOP-lowering efficacy of both brinzolamide and levobetaxolol.

The study was approved for each study site by the appropriate Institutional Review Board or Institutional Ethics Committee and the parents or legal representatives read, signed, and dated an Institutional Review Board/Institutional Ethics Committee approved consent form prior to their child's participation in the study.

Eligible patients were of any race and either gender. They were younger than 6 years of age at the time of the screening visit, and they had a clinical diagnosis of glaucoma or ocular hypertension and required IOP-lowering in the opinion of the treating ophthalmologist. Patients under treatment with ocular hypotensive medication(s) at the time of enrollment and untreated patients were eligible for enrollment. There was no washout of prior medications, because it was felt that a washout period of adequate duration (eg, 28 days for timolol) might expose patients to an unacceptable risk. Because patients with IOPs controlled by an ocular hypotensive medication prior to the study were eligible for enrollment without a washout of the previous medication(s), there was no minimum IOP requirement for eligibility; however, patients with IOPs exceeding 36 mm Hg were not eligible for enrollment. Because a substantial number of pediatric glaucoma patients are aphakic and wear contact lenses, contact lens use was allowed during the study. Removal of extended wear contact lenses for instillation of medication was not required as parents of aphakic children typically instill topical medication with the lenses in place. All contact lens–wearing children were provided with new contact lenses at the time of enrollment.

Patients were excluded from the study for any of the following reasons: 6 years of age or older at the time of screening; at or below the 5th percentile for body weight (applied to children <1 year of age only); intraocular surgery within the past 30 days in the study eye; clinically significant or progressive retinal disease in the study eye; ocular or systemic diseases precluding administration of a topical beta-blocker or carbonic anhydrase inhibitor; any eye with a history of penetrating keratoplasty; any amount of congenital optic atrophy in the study eye; fewer than 3 weeks stable dosing (prior to the screening visit) of current IOP-lowering medication(s) or of drugs for hyperkinesis (eg, clonidine); any abnormality preventing reliable applanation tonometry; hypersensitivity to topical or systemic beta-blockers, carbonic anhydrase inhibitors, sulfonamides, or any component of either of the study medications; therapy with another investigational agent within 30 days of study start; use of any other topical or systemic ocular hypotensive medication during the study.

Patient enrollment was stratified into four age groups: (1) 1 week to less than 1 year; (2) 1 year to less than 2 years; (3) 2 years to less than 4 years; and (4) 4 years to less than 6 years. These age strata, the number of patients planned, and the numbers actually enrolled are provided in Table 1. Patients were to be randomized to the two treatment groups in a 1:1 ratio according to computer-generated schedules prepared by the biostatistics group at Alcon Research, Ltd. (Alcon). Four distinct series were generated for each investigator, corresponding to the four age groups. The study was double-masked and all study medications were supplied in identical 5 mL opaque dropper bottles identified by the patient randomization number.

There were two prerandomization visits: screening and baseline, 1 week later. Patients being treated with a prestudy IOP-lowering medication continued that medication between the screening and baseline visits, receiving their final dose of prestudy medication the day before the baseline visit.

Patients meeting inclusion and exclusion criteria at the screening and baseline visits were assigned a patient number. Parents were instructed to instill a single drop in each study eye at approximately 8 AM and 8 PM. Twice daily dosing is the labeled adult dosage for levobetaxolol; however, brinzolamide is approved as a three times daily drug in the United States. Because twice daily and three times daily dosing of brinzolamide are known to provide similar IOP-lowering efficacy,[16] to reduce

compliance problems for working parents, and for masking purposes, brinzolamide was administered twice daily in this study. Study patients were scheduled for visits after 2, 6, and 12 weeks on study drug.

IOP was measured either with a Tono-Pen® tonometer (Reichert Inc., Depew, NY) or by Goldmann or Perkins applanation tonometry at all visits at approximately 9 AM. Each eye was measured twice and the measurements were averaged. The same tonometry method was used for any given patient throughout the study. If an examination under anesthesia was necessary to obtain IOPs, measurements were generally only obtained at the screening and exit visits. For any patient, the same type of anesthesia was used for both visits. IOP measurements were taken as soon as adequate sedation was attained.[18] Additional exams under anesthesia were not required but could have been performed at the discretion of the investigators. Visual acuity was measured at all visits using developmentally appropriate procedures. A single technique was used consistently for each child. Ocular features, patient alertness, pulse, systolic and diastolic blood pressure, changes in medications, and adverse events were collected at all visits. Patient alertness was assessed using the Observer's Assessment of Alertness Scale.[19,20] A dilated fundus examination and measurement of corneal diameter were carried out at the patient's screening and exit visit. The determination of the relationship of adverse events to study drug was made by the investigators.

Statistical Methods

This study was designed to be descriptive. The primary efficacy parameter was an assessment of mean IOP change from baseline at 9 AM. Study visits were planned at weeks 2, 6, and 12. If only one of a patient's eyes was dosed, the dosed eye was selected for analysis. If both eyes were dosed, the worse evaluable eye was selected for analysis.

The primary analytic method consisted of describing the IOP data with means and two-sided 95% confidence intervals. Repeated measures analysis of variance was used to estimate the means and confidence intervals. Descriptive statistics were calculated for IOP, IOP change from baseline, and IOP percent change from baseline.

All patients who received study medication and had at least one on-therapy visit were considered evaluable for intent-to-treat analysis and included in the intent-to-treat data set. Evaluability for all patients and visits was determined prior to breaking the code for masked treatment assignment.

Results

Eighty patients (32 randomized to brinzolamide and 48 to levobetaxolol) were enrolled in the study and received study medication. The imbalance between the two treatment groups was the result of very low enrollment at the majority of the study sites. Four unique randomization sequences, corresponding to the four age groups, had been prepared for each study site. To complete a block of both treatments, at least two patients in a given age stratum would be needed at a study site. Since this did not occur at many sites, an imbalance in the randomization to treatment developed, and enrollment had to continue until the minimum number of patients had been attained for all treatment group/age strata combinations. Of these, two (both in the levobetaxolol group) were discontinued from the study prior to collection of any scheduled on-therapy study visit data (Patient 2910.3501, due to inadequate IOP control; Patient 3614.1221, because of an inclusion/exclusion violation [IOP exceeded 36 mm Hg at baseline]); therefore, 78 patients were evaluable for and included in the intent-to-treat analysis. An additional patient in the levobetaxolol group completed the study, but IOPs were not successfully collected at any of the visits as the patient was uncooperative and anesthesia was not used. However, safety data were collected through week 12. Fourteen (including the 2 noted above) of the 80 enrolled (6 in brinzolamide group and 8 in the levobetaxolol group) discontinued the study prematurely. The most common reason for patient discontinuation was inadequate control of IOP (five in the brinzolamide group and six in the levobetaxolol group). Discontinuation rates and reasons for discontinuation were similar between the two treatment groups.

Demographic data for the study population are given in Table 2. The age distribution was 28 days to 5 years (mean age for brinzolamide and levobetaxolol was 2.6 and 2.4 years, respectively). Treatment groups were similar with no statistically significant differences in the distribution of patients regarding age category, sex, race, iris color, or glaucoma diagnosis, although numerical differences between the two groups in terms of sex and glaucoma diagnosis trended toward significance ($p = 0.0781$ and $p = 0.0961$, respectively).

Changes from Baseline

Baseline mean IOP was similar for the two treatment groups when considering all of the patients. Baseline IOP was also similar for the treatment groups subdivided into those patients without a prestudy therapy and those on a prior treatment (Table 3). Both brinzolamide and levobetaxolol demonstrated clinically relevant IOP reductions for those patients entering the study without a prestudy treatment (Figure 1). For brinzolamide, the peak mean IOP decrease from baseline was 5.0 mm Hg at week 6. For levobetaxolol the peak reduction was 4.0 mm Hg at week 2.

Because the study allowed enrollment of patients either on or not on an IOP-lowering medication at the time of randomization, an evaluation of the change in IOP from baseline should discriminate between these two subpopulations. Sixty-nine percent of the brinzolamide patients and 62% of the levobetaxolol patients were being treated with one or more IOP-lowering medications at the study start.

For the brinzolamide patients on IOP-lowering medication(s) at the time of enrollment, IOP increased slightly (approximately 1.5 to 2 mm Hg) over the study. For the levobetaxolol patients on a prestudy therapy, IOP de-

Table 2. Patient demographics by treatment group

	Total		Brinzolamide		Levobetaxolol		
	N	%	N	%	N	%	*p*-value[a]
Total	80	100	32	100	48	100	
Age							
1 week to <1 year old	15	19	6	19	9	19	0.8101
1 year to <2 years old	15	19	5	16	10	21	
2 years to <4 years old	27	34	10	32	17	35	
4 years to <6 years old	23	29	11	34	12	25	
Sex							
Male	47	59	15	47	32	67	0.0781
Female	33	41	17	53	16	33	
Race							
Asian	35	44	15	47	20	42	0.9763
Black or African American	9	11	3	9	6	13	
Caucasian	27	34	10	31	17	35	
Multiracial	2	3	1	3	1	2	
Other	8	10	3	9	5	10	
Iris color							
Blue	12	15	3	9	9	19	0.8113
Brown	61	76	27	84	34	71	
Green	1	1	0	0	1	2	
Gray	3	4	1	3	2	4	
Hazel	2	3	1	3	1	2	
No iris[b]	1	1	0	0	1	2	
Diagnosis							
Ocular hypertension	1	1	1	3	0	0	0.0961
Primary congenital glaucoma	32	40	17	53	15	31	
Primary glaucoma associated with systemic or ocular abnormalities	19	24	6	19	13	27	
Secondary glaucoma	28	35	8	25	20	42	

[a]*p*-value from χ^2 or Fisher's exact test.
[b]Patient 1641.9001 had aniridia.

Table 3. Baseline IOP (mmHg) comparison

	Baseline average[a]		
	Mean	SD	N
All patients			
Brinzolamide	24.8	5.8	32
Levobetaxolol	24.5	5.4	46
Prior IOP-lowering therapy			
Brinzolamide	24.5	6.6	22
Levobetaxolol	23.3	5.8	29
No prior therapy			
Brinzolamide	25.5	3.8	10
Levobetaxolol	26.6	3.9	17

SD: standard deviation.
[a]Baseline average = average of the screening and baseline visits if both values for both visits were reported; otherwise, the single reported value was used.

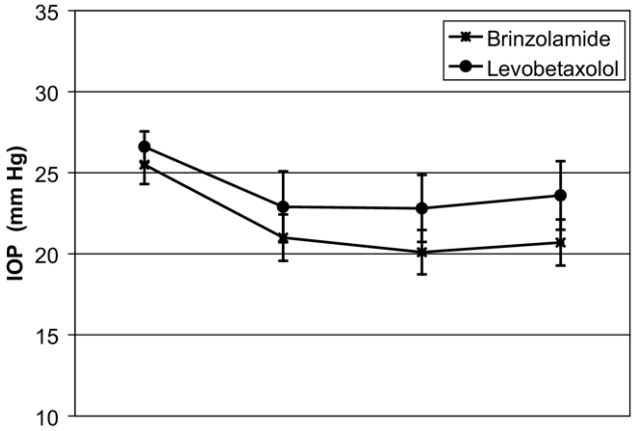


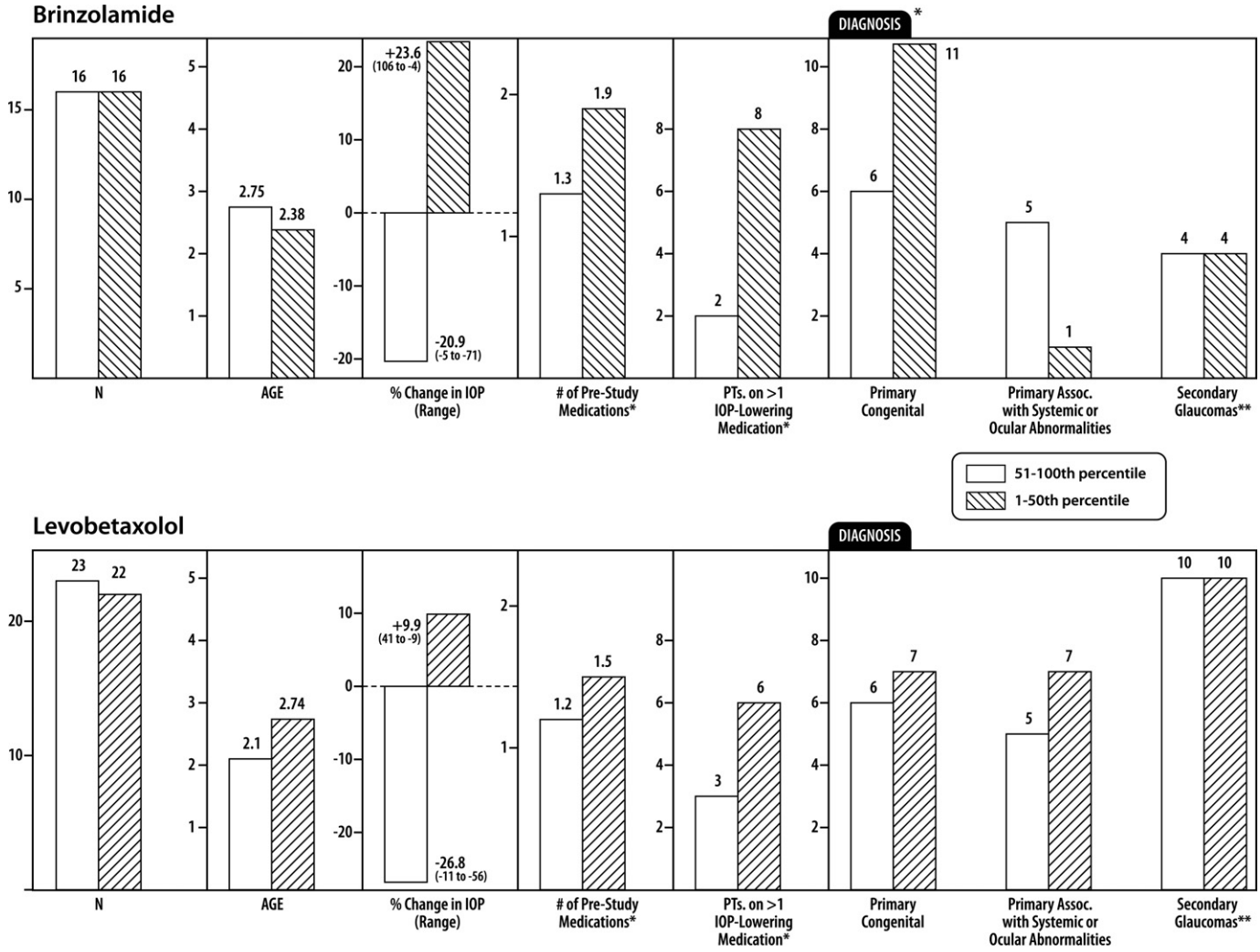
FIG 1. Mean IOP for brinzolamide and levobetaxolol. Patients not on a prestudy IOP-lowering therapy. *IOP:* intraocular pressure. Error bars are ±1 standard error.

creased modestly (1.6 mm Hg at week 12). Prestudy treatment included all available classes of IOP-lowering drugs, with beta-adrenergic blockers being most commonly employed (see e-Supplement 2, available at jaapos.org). The mean number of prestudy IOP-lowering medications per patient (for patients on such therapy) was 1.6 for the brinzolamide treatment group and 1.4 for levobetaxolol treatment group.

Among all patients in the intent-to-treat data set treated with brinzolamide, the peak mean IOP decrease from baseline was 1.0 mm Hg at week 6. Among patients treated with levobetaxolol, the peak mean IOP decrease from baseline was 2.9 mm Hg at week 2.

Response in Specific Subgroups

Patient response to therapy was different for the two products depending on the type of glaucoma, and whether



*One patient randomized to brinzolamide was diagnosed as ocular hypertension. Forty-eight patients were randomized to levobetaxolol. Two of these discontinued the study prior to collection of any on-therapy data. A third patient completed the study but IOPs were never successfully collected after the baseline visit.
**Secondary glaucoma includes 1 traumatic glaucoma patient (levobetaxolol group). All others were secondary to aphakia.

FIG 2. Patient characteristics for top 50% by IOP response (open bars) and bottom 50% by IOP response (hatched).

or not there had been prestudy IOP-lowering therapy. Ranking patients by individual response to treatment (% change in IOP from baseline at the exit visit) and then dividing each treatment group into halves results in two groups: those with a better response to therapy (top 50%), and those who responded poorly (bottom 50%) (see e-Supplement 3, available at jaapos.org). This allows comparison of the relative frequency of different glaucoma diagnoses, prior IOP-lowering medication, number of prestudy IOP-lowering medications, and patient age between these two broad patient classifications. Figure 2 summarizes the characteristics of these patient groups. For the brinzolamide top 50% response group ("responders"), the mean % IOP change from baseline was a decrease of 21%. For the bottom 50% ("nonresponders") of brinzolamide patients, the mean % IOP change from baseline was an increase of 24%. The levobetaxolol responders had a mean percentage reduction of 27%, while the nonresponders showed an average increase of 10%. The mean age was similar between both subgroups for brinzolamide (2.75 years vs 2.38 years, $p = 0.56$, Student's t-test) and for levobetaxolol (2.09 years vs 2.74 years, $p = 0.21$). The glaucoma diagnosis for each patient was categorized as primary congenital; glaucoma associated with ocular or systemic abnormalities, including Axenfeld-Rieger, Peter's anomaly, aniridia, Sturge-Weber, and microspherophakia; and secondary glaucoma, all of which were following cataract surgery and were aphakic except for one patient with traumatic glaucoma. Each of these categories was distributed essentially evenly between the upper and lower 50% of patients for levobetaxolol, allowing no prediction to be made regarding efficacy in individual patients based on diagnosis. In contrast, approximately two-thirds of the primary congenital patients in the brinzolamide group were found in the bottom 50%, with only 6 of 17 (35%) in the top 50% (Figure 2). For glaucoma associated with systemic or ocular abnormal-

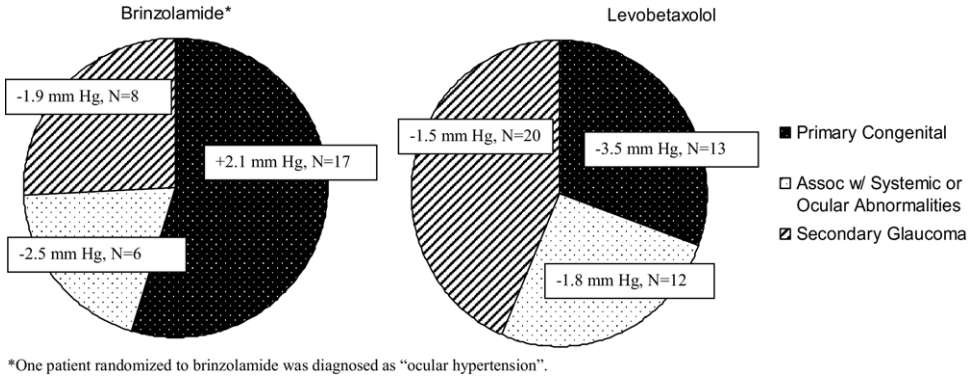


FIG 3. Mean IOP reduction at week 12 (or early exit) by diagnosis.

ities, an even more skewed distribution was apparent; five of six (83%) were part of the top 50% in IOP response.

Figure 3 shows each of the three diagnostic classes for each treatment group, with the mean IOP at exit for each. For brinzolamide, it is apparent that the medication is most effective in treating glaucoma associated with systemic or ocular abnormalities (IOP change = −2.5 mm Hg) and least effective with primary congenital glaucoma (+2.1 mm Hg). On the other hand, levobetaxolol provides some therapeutic benefit for all three classes: primary congenital glaucoma (−3.5 mm Hg), secondary glaucomas (−1.5 mm Hg), glaucoma associated with systemic or ocular abnormalities (−1.8 mm Hg).

Safety Evaluation

The evaluation of safety was based on all patients (N = 80) who were enrolled in the study and received at least one dose of study medication. No concerns were identified with regard to visual acuity, the adnexae, anterior segment, posterior segment, vitreous, patient alertness, and cardiovascular parameters. A total of eight patients (five in the brinzolamide group and three in the levobetaxolol group) experienced an increase in corneal diameter of at least 1 mm in at least one eye. Two (both in the brinzolamide group) were considered to be clinically relevant and were recorded as adverse events by the investigators. IOP for both of these patients had increased substantially from baseline. Adverse events in the overall safety population were predominately nonserious and generally mild to moderate in intensity. No patient experienced a serious adverse event that was related to study drug. Adverse events judged to be related to treatment are tabulated in Table 4. Of the 80 enrolled patients, 14 discontinued the study early. The most frequent reason for discontinuation was inadequate control of IOP (5 brinzolamide, 6 levobetaxolol). Other reasons for discontinuation were parent decision unrelated to an adverse event (1), inclusion/exclusion violation—ineligible baseline IOP (1), and patient dispensed expired study medication (1). No patients in either treatment group discontinued due to an adverse event.

Table 4. Adverse events related to therapy (all patients)

	Brinzolamide N = 32		Levobetaxolol N = 48	
Adverse event	N	%	N	%
Ocular				
Hyperemia eye	1	3.1	1	2.1
Discharge eye	1	3.1	1	2.1
Discomfort eye	1	3.1	1	2.1
Tearing	1	3.1		
Foreign body sensation			1	2.1
Hordeolum			1	2.1
Pruritus eye			1	2.1
Body as a whole				
Fatigue	1	3.1		
Cardiovascular system				
Bradycardia	1	3.1	1	2.1

Discussion

It is clear from the data that brinzolamide and levobetaxolol, both dosed twice daily, provided IOP-lowering benefits to patients with pediatric glaucomas. Patients entering the study on IOP-lowering therapy (average number of medications was approximately 1.5) could have three different outcomes after switching to study medication. Their IOP could remain unchanged, indicating that the study drug was providing at least as much control as prior therapy; their IOP could drop, indicating better control by the study drug; their IOP could increase, indicating that the study drug was not as effective as prior therapy. We have focused on the exit IOP (taken at 12 weeks for patients completing the study), because, by that time, there should be no lingering effects of prior therapy on IOP (eg, ref. [21]). For the brinzolamide patients on a prior therapy, IOP was relatively unchanged during the study with mean IOP change from baseline ranging from −1.2 to +1.9 mm Hg over all visits. For levobetaxolol patients on a prior therapy, IOP tended to decrease after switching to study drug with mean IOP change from baseline ranging from −1.1 to −2.7 mm Hg over all visits.

It is probably easier to reach a conclusion regarding the efficacy of these drugs when considering only those patients with no prior IOP-lowering medication. Both brin-

zolamide and levobetaxolol provided clinically relevant IOP lowering in this subgroup. Brinzolamide lowered IOP between 4 and 5 mm Hg (16–20%) in these patients, a level of efficacy comparable to that reported in adults.[15,22] Levobetaxolol provided up to a 4 mm Hg (15%) decrease in these patients. Caution should be taken in interpreting these results as the number of patients entering this study without a prestudy therapy was small. There were 10 such patients in the brinzolamide group and 16 in the levobetaxolol group.

Dorzolamide is another topical carbonic anhydrase inhibitor recently evaluated in children of similar age.[11] Interestingly, the authors of the dorzolamide study reported an approximate 7 mm Hg reduction in IOP from baseline. Brinzolamide and dorzolamide have generally been shown to have equivalent efficacy in adult glaucoma studies.[15,16] There are several differences in the two studies that may account for the different results. First, mean baseline IOP was substantially higher in the dorzolamide study (approximately 28 mm Hg for patients <2 years; approximately 33 mm Hg for patients ≥2 years) than in the present study (24 mm Hg). If percentage decrease in IOP from baseline is considered instead of absolute mm Hg, the results of the two studies are more similar. Second, in the present study there was no washout of prestudy IOP-lowering medication, because it was felt that this would represent an unnecessary risk to these patients. In the dorzolamide study there was a minimum 24-hour washout for all patients, with up to a 21-day washout at the discretion of the investigators. As noted previously, IOP-lowering efficacy is much easier to demonstrate in patients who have not been under treatment with an IOP-lowering therapy.

Recognizing that pediatric glaucoma includes a plethora of distinct diseases/conditions, several investigators have attempted to identify those patients most likely to benefit from a given IOP-lowering medication based on diagnosis. For example, Boger and Walton[8] found that timolol provided at least a modest benefit for patients with several categories of glaucoma, including primary congenital, aniridia, and congenital rubella syndrome. Enyedi and Freedman[5] found that latanoprost could be of benefit to patients with juvenile open-angle glaucoma and aphakic glaucoma but was of limited or no benefit for several other disease classes including Sturge-Weber and primary congenital glaucomas. Awad et al[23] reported successful medical treatment of Sturge-Weber patients with betaxolol in conjunction with either dipivefrin or pilocarpine. Similarly, in the present study we have found trends that suggest that outcome may be at least, in part, dependent on the diagnosis. For brinzolamide, the drug was less effective in this study for those patients with primary congenital glaucoma. On the other hand, for patients with glaucoma attributed to systemic or ocular abnormalities, brinzolamide was effective in five of six patients.

As noted above, eight patients (five in the brinzolamide group and three in the levobetaxolol group) experienced an increase in corneal diameter of at least 1 mm in at least one eye. Two (both in the brinzolamide group) were considered to be clinically relevant and were recorded as adverse events by the investigators. The pediatric use section of the product labeling in the United States for brinzolamide includes the statement that "five out of 32 patients demonstrated an increase in corneal diameter of one millimeter." Closer examination of these five patients shows a range of ages (two less than one year old; one 1-year-old; one 2-year-old; and one 4-year-old), and of diagnoses (one Sturge-Weber; three primary congenital; and one ocular hypertension). The percent change in IOP at exit relative to baseline for these patients ranged from −31% to +55%. It is thus difficult to correlate these observed corneal diameter increases with lack of IOP control, with patient age, or with a specific glaucoma diagnosis.

A strength of randomized clinical trials is that they are usually designed to include a very well-defined study population such that confounding variables are minimized, thereby facilitating analysis and interpretation of the study results. At odds with the need to minimize variability in the enrolled patients are two factors of particular relevance to a study of IOP-lowering medications in children: patient safety and the rarity of the disease. For safety reasons, certain study design elements common in adult studies were relaxed or omitted in this pediatric study.

There are a number of limitations to this study. These include the relatively small number of patients when compared with adult studies, the brief time on drug (12 weeks), and the variability in the study population. In addition, certain adverse events which are routinely collected in adult studies (eg, stinging) are difficult if not impossible to collect from preverbal children. Despite these limitations, this study provides supportive evidence for the safety of both brinzolamide and levobetaxolol in the pediatric glaucoma population less than 6 years of age. Both of these drugs were found to be well tolerated over the course of this study. In addition, both were found to maintain IOP control in those patients entering the study on an IOP-lowering medication and to provide clinically relevant IOP reduction in those patients entering without a prior IOP-lowering medication.

The results of this trial provide important useful information for the future management of children with challenging diagnoses of primary congenital glaucoma, glaucoma associated with ocular and systemic abnormalities, and secondary glaucoma.

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e-Supplement 1. The Brinzolamide Pediatric Study Group

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e-Supplement 2. Prestudy IOP-lowering therapy

	Treatment group	
Monotherapy	Brinzolamide	Levobetaxolol
Beta-adrenergic antagonist	10	14
Carbonic anhydrase inhibitor (CAI)	0	1
Prostaglandin analogue (PGA)	2	3
Alpha-adrenergic agonist	0	1
Multiple medications*		
Beta-adrenergic antagonist + CAI	2	4
Beta-adrenergic antagonist + Pilocarpine	3	3
Beta-adrenergic antagonist + PGA	1	3
Beta-adrenergic antagonist + Alpha agonist	1	0
Beta-adrenergic antagonist + CAI + PGA	2	0
Beta-adrenergic antagonist +CAI + Pilocarpine	1	0
Total	22	29

*Beta-adrenergic antagonist + CAI includes individual drugs dosed separately, and the fixed combination of dorzolamide and timolol.

e-Supplement 3. Study patients listed by treatment in rank order of IOP response

Patient	Treatment	IOP change (%)	Diagnosis*	Age (years)	No. IOP-lowering medications at screening
5031	Brinzolamide	−71	Secondary glaucoma (aphakia)	4	0
312	Brinzolamide	−48	Primary congenital glaucoma	1	1 betaxolol
421	Brinzolamide	−35	Primary glaucoma associated with systemic or ocular abnormalities (Axenfeld-Rieger)	3	1 timolol
6531	Brinzolamide	−33	Ocular hypertension*	5	0
611	Brinzolamide	−28	Primary congenital glaucoma	1	0
713	Brinzolamide	−26	Primary congenital glaucoma	1	1 betaxolol
6031	Brinzolamide	−18	Primary glaucoma associated with systemic or ocular abnormalities (aniridia)	4	2 betaxolol; latanoprost
532	Brinzolamide	−14	Primary glaucoma associated with systemic or ocular abnormalities (aniridia)	5	1 betaxolol
1031	Brinzolamide	−14	Primary congenital glaucoma	5	0
7522	Brinzolamide	−12	Secondary glaucoma (aphakia)	3	3 latanoprost; dorzolamide; timolol
602	Brinzolamide	−8	Primary congenital glaucoma	<1	0
7531	Brinzolamide	−7	Primary glaucoma associated with systemic or ocular abnormalities (Sturge-Weber)	4	1 latanoprost
9501	Brinzolamide	−6	Primary glaucoma associated with systemic or ocular abnormalities (Sturge-Weber)	<1	1 timolol
522	Brinzolamide	−5	Secondary glaucoma (aphakia)	3	1 betaxolol
502	Brinzolamide	−5	Primary congenital glaucoma	<1	1 timolol
3031	Brinzolamide	−5	Secondary glaucoma (aphakia)	5	0
5022	Brinzolamide	−4	Primary congenital glaucoma	3	0
322	Brinzolamide	−4	Secondary glaucoma (aphakia)	3	0
701	Brinzolamide	0	Primary congenital glaucoma	<1	3 pilocarpine; dorzolamide; timolol
603	Brinzolamide	0	Primary congenital glaucoma	<1	0
1531	Brinzolamide	4	Secondary glaucoma (aphakia)	4	0
431	Brinzolamide	7	Primary congenital glaucoma	1	1 brimonidine
721	Brinzolamide	16	Primary congenital glaucoma	2	3 pilocarpine; dorzolamide; timolol
1522	Brinzolamide	17	Primary glaucoma associated with systemic or ocular abnormalities (Sturge-Weber)	3	1 bimatoprost
301	Brinzolamide	18	Primary congenital glaucoma	<1	2 betaxolol; pilocarpine
331	Brinzolamide	20	Primary congenital glaucoma	4	1 betaxolol
2031	Brinzolamide	29	Secondary glaucoma (aphakia)	5	2 dorzolamide; timolol
6022	Brinzolamide	33	Primary congenital glaucoma	2	3 latanoprost; dorzolamide; timolol
121	Brinzolamide	36	Secondary glaucoma (aphakia)	3	1 timolol
712	Brinzolamide	45	Primary congenital glaucoma	1	2 timolol; pilocarpine
221	Brinzolamide	55	Primary congenital glaucoma	2	2 timolol; pilocarpine
5531	Brinzolamide	106	Primary congenital glaucoma	5	2 betaxolol; brimonidine
7521	Levobetaxolol	−56	Primary congenital glaucoma	3	0
7511	Levobetaxolol	−52	Primary glaucoma associated with systemic or ocular abnormalities (aniridia)	1	2 betaxolol; latanoprost
702	Levobetaxolol	−50	Primary congenital glaucoma	<1	1 betaxolol
6521	Levobetaxolol	−48	Secondary glaucoma (aphakia)	3	0
3033	Levobetaxolol	−40	Secondary glaucoma (aphakia)	5	0
722	Levobetaxolol	−36	Primary congenital glaucoma	2	0
711	Levobetaxolol	−30	Primary congenital glaucoma	1	1 betaxolol
6021	Levobetaxolol	−29	Secondary glaucoma (aphakia)	3	2 dorzolamide; timolol
8501	Levobetaxolol	−29	Primary glaucoma associated with systemic or ocular abnormalities (aniridia)	1	0
1411	Levobetaxolol	−26	Secondary glaucoma (aphakia)	1	2 dorzolamide; timolol
531	Levobetaxolol	−26	Secondary glaucoma (traumatic glaucoma)	5	0
511	Levobetaxolol	−23	Primary congenital glaucoma	1	1 timolol
6001	Levobetaxolol	−21	Primary congenital glaucoma	<1	1 betaxolol
323	Levobetaxolol	−21	Secondary glaucoma (aphakia)	3	0
422	Levobetaxolol	−19	Secondary glaucoma (aphakia)	2	1 levobunolol
7001	Levobetaxolol	−19	Primary glaucoma associated with systemic or ocular abnormalities (Axenfeld-Rieger)	<1	0
521	Levobetaxolol	−17	Primary glaucoma associated with systemic or ocular abnormalities (Axenfeld-Rieger)	3	1 timolol
1511	Levobetaxolol	−17	Primary congenital glaucoma	1	1 timolol
6501	Levobetaxolol	−14	Primary glaucoma associated with systemic or ocular abnormalities (Peter's anomaly)	<1	1 dorzolamide
7532	Levobetaxolol	−11	Primary congenital glaucoma	5	1 latanoprost

e-Supplement 3. Study patients listed by treatment in rank order of IOP response

Patient	Treatment	IOP change (%)	Diagnosis*	Age (years)	No. IOP-lowering medications at screening
601	Levobetaxolol	−11	Secondary glaucoma (aphakia)	<1	1 betaxolol
1021	Levobetaxolol	−11	Secondary glaucoma (aphakia)	3	1 brimonidine
3032	Levobetaxolol	−11	Secondary glaucoma (aphakia)	5	0
9001	Levobetaxolol	−9	Primary glaucoma associated with systemic or ocular abnormalities (aniridia)	<1	1 betaxolol
533	Levobetaxolol	−9	Secondary glaucoma (aphakia)	5	2 timolol; pilocarpine
1231	Levobetaxolol	−8	Primary glaucoma associated with systemic or ocular abnormalities (Sturge-Weber)	4	1 travoprost
5032	Levobetaxolol	−7	Primary glaucoma associated with systemic or ocular abnormalities (Sturge-Weber)	4	0
6032	Levobetaxolol	−6	Primary congenital glaucoma	4	2 betaxolol; latanoprost
501	Levobetaxolol	−5	Primary glaucoma associated with systemic or ocular abnormalities (Sturge-Weber)	<1	1 betaxolol
2131	Levobetaxolol	−4	Secondary glaucoma (aphakia)	5	0
333	Levobetaxolol	−3	Primary congenital glaucoma	5	1 latanoprost
321	Levobetaxolol	5	Secondary glaucoma (aphakia)	2	0
432	Levobetaxolol	7	Primary congenital glaucoma	1	1 timolol
703	Levobetaxolol	8	Secondary glaucoma (aphakia)	<1	1 betaxolol
332	Levobetaxolol	14	Primary glaucoma associated with systemic or ocular abnormalities (Axenfeld-Rieger)	5	0
723	Levobetaxolol	14	Secondary glaucoma (aphakia)	3	0
8021	Levobetaxolol	14	Secondary glaucoma (aphakia)	5	0
3021	Levobetaxolol	15	Secondary glaucoma (aphakia)	3	0
5121	Levobetaxolol	17	Primary congenital glaucoma	3	2 dorzolamide; timolol
5111	Levobetaxolol	19	Secondary glaucoma (aphakia)	1	2 dorzolamide; timolol
122	Levobetaxolol	20	Primary glaucoma associated with systemic or ocular abnormalities (aniridia)	3	2 timolol; pilocarpine
1521	Levobetaxolol	24	Secondary glaucoma (aphakia)	3	1 betaxolol
2121	Levobetaxolol	35	Secondary glaucoma (aphakia)	2	0
311	Levobetaxolol	36	Primary congenital glaucoma	1	1 betaxolol
222	Levobetaxolol	41	Primary glaucoma associated with systemic or ocular abnormalities (microspherophakia)	3	2 timolol; pilocarpine

*Investigators placed patients into general diagnostic categories. More specific diagnoses are given in parentheses wherever possible.