Effect of Brinzolamide and Dorzolamide on Aqueous Humor Flow in Human Eyes

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• PURPOSE: To measure the relative efficacy of brinzolamide hydrochloride 1% ophthalmic suspension, a new carbonic anhydrase inhibitor, compared with the currently used dorzolamide hydrochloride 2% ophthalmic solution as suppressors of aqueous humor flow in human eyes, and to study the difference of effect during the day and at night.

• METHODS: A randomized, double-masked, placebo-controlled study of 25 normal human subjects was carried out at Mayo Clinic. The daytime rate of aqueous humor flow was measured every 2 hours from 8 AM to 4 PM by means of fluorophotometry. Likewise, the nighttime rate of aqueous humor flow was measured every 2 hours from 12 AM to 6 AM. Intraocular pressure was measured at 4 PM and 6 AM.

• RESULTS: Brinzolamide reduced aqueous flow by 0.47 ± 0.20 μl per min (mean ± SD) during the day, whereas dorzolamide reduced flow by 0.34 ± 0.20 μl per min. Brinzolamide reduced aqueous flow by 0.16 ± 0.12 μl per min during the night, whereas dorzolamide reduced flow by 0.10 ± 0.13 μl per min. Brinzolamide reduced afternoon intraocular pressure by 1.5 ± 1.1 mm Hg, and dorzolamide reduced afternoon intraocular pressure by 1.1 ± 1.0 mm Hg. Brinzolamide reduced the morning awakening intraocular pressure by 0.3 ± 1.6 mm Hg, and dorzolamide reduced it by 0.8 ± 1.0 mm Hg.

• CONCLUSIONS: Our data support the idea that brinzolamide is at least as efficacious as dorzolamide as a suppressor of aqueous humor flow in normal human eyes and that there is probably not a clinically significant difference between the two drugs in this efficacy. Clinicians who prescribe brinzolamide should expect similar ocular hypotensive responses from brinzolamide and dorzolamide. (Am J Ophthalmol 1999;128:292–296.

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CARBONIC ANHYDRASE INHIBITORS ARE USED AS ocular hypotensive agents for the treatment of glaucoma. These agents have been administered systemically and are known to reduce intraocular pressure in normal and glaucomatous persons by reducing the rate of aqueous humor formation.[1–6] The side effects of systemic administration have stimulated the successful development of topical carbonic anhydrase inhibitors.[7]

Dorzolamide hydrochloride (Trusopt; Merck & Co, West Point, Pennsylvania) was the first topical carbonic anhydrase inhibitor approved for the treatment of glaucoma.[7] This drug is now widely used as an adjunctive treatment for glaucoma with other classes of drugs, such as beta-adrenergic antagonists, alpha-adrenergic agonists, cholinergics, and synthetic prostaglandins. In previous studies of the aqueous-suppressing efficacy of dorzolamide, the drug was found to be approximately half as efficacious as orally administered acetazolamide,[8,9] to be additive to the hypotensive effect of beta-adrenergic antagonists,[8] and to be weakly effective at night during sleep, in contrast to beta-adrenergic antagonists that have no measurable effect.[10]

Brinzolamide 1% ophthalmic suspension (Azopt; Alcon Laboratories, Fort Worth, Texas) is the second topical carbonic anhydrase inhibitor to have been approved by the United States Food and Drug Administration for treatment of glaucoma. The limited written information about this drug in the public domain has been in abstracts.[11–18] A recent study reported that brinzolamide has an effect similar to that of dorzolamide but causes less discomfort.[19] Of potential interest to clinicians would be a comparative study of the efficacy of these two drugs as suppressors of aqueous humor flow both during the day and at night during sleep.

PATIENTS AND METHODS

THE STUDY WAS CARRIED OUT AT MAYO CLINIC, ROCHESter, Minnesota. Twenty-five normal human volunteers

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with two eligible eyes were recruited. Of the twenty-five, 13 were women and 12 were men; all were between the ages of 23 and 42 years (mean, 32 years). Subjects underwent an eligibility examination that consisted of a medical and ophthalmic history, biomicroscopy, visual acuity measurement, applanation tonometry, and ophthalmoscopy. Exclusion criteria were as follows: allergy or contraindication to fluorescence or sulfonamide derivative; narrow palpebral fissures; photophobia demonstrated on slit-lamp examination; women who were pregnant or nursing; use of systemic beta-blockers; and any ocular disease or previous ocular surgery. The women were required to have a negative pregnancy test within 48 hours of the beginning of each session of the study. Subjects who met the eligibility criteria gave written informed consent in accordance with United States federal guidelines for investigation of human subjects. The study was approved by the institutional review board at Mayo Clinic.

At the time of enrollment, corneal and anterior chamber autofluorescence and the volume of the anterior chamber were measured, and the measurements were used subsequently in the calculation of aqueous humor flow.[20,21]

Every subject had two eligible eyes. For each subject, one eye was randomly designated the drug-treated eye. The other eye was designated the placebo-treated eye. These designations were maintained for the duration of the study.

The study consisted of three sessions. At least 2 weeks elapsed between each session to allow one drug to disappear completely before the next was tested. The drug-treated eye was treated in each of the three sessions with placebo, brinzolamide, or dorzolamide; the sequence of these treatments was determined by random assignment. The placebo-treated eye received a placebo in all three sessions. Artificial tears ophthalmic solution (Hypotears; IOLab, Johnson & Johnson, Claremont, California) served as the placebo.

The drugs (including placebo) were administered at 5:15 PM on the day before the measurement of aqueous flow and at 8:00 AM, 4:00 PM, and 10:30 PM on the day of the measurement of flow.

Sterile dropper bottles containing brinzolamide 1%, dorzolamide 2%, or placebo were prepared by the Mayo Pharmacy. All bottles contained 1.5 ml of solution. All labels and bottles were identical in appearance. However, brinzolamide is a suspension and dorzolamide is a solution. Thus, masking of the technician who measured aqueous flow and intraocular pressure was maintained by having a third person administer the drugs; subjects were not allowed to see the drops and were unaware of this difference in appearance. The bottles were labeled as follows: "Session 1, Subject 1, Right Eye," "Session 1, Subject 1, Left Eye," "Session 1, Subject 2, Right Eye," and so on. The data were not stratified according to drug until all the data were recorded and stored in a computer spreadsheet. Correct labeling of the dropper bottles was confirmed after the study by visualization of the suspension and by absorption spectroscopy of the solutions.

Fluorescein, the tracer, was self-administered by each subject before each of the three study sessions. Before each measurement, the adequacy of the concentration of fluorescein in the cornea and anterior chamber was confirmed by fluorophotometry.

The chance of an error of administration of any drug or placebo was minimized by having these administered by the third-party technician. All doses of drugs were administered from dropper bottles that deliver 40 to 70 μl per drop. The subjects were required to close their eyes for 2 minutes after each instillation. Separate tissues were used to blot each eye after drug instillation to avoid transferring drug from one eye to the other.

The drugs (including placebo) were administered at 5:15 PM the day before the measurement of aqueous flow. At 2:00 AM the morning of the study, subjects instilled 3 to 5 drops of fluorescein 2% into each eye. Younger subjects instilled more drops to obtain adequate concentrations of fluorescein in the ocular tissue.

Subjects reported again to the test area at 7:45 AM. Fluorophotometric measurements were taken every 2 hours from 8:00 AM to 4:00 PM for a total of five daytime measurements. After the 8:00 AM fluorophotometric measurement, subjects received a second dose of drug and placebo.

After the 4:00 PM fluorophotometric measurement, the intraocular pressure was measured in both eyes with a pneumatonometer. This measurement was followed by a third instillation of drug and placebo and a second administration of fluorescein.

At 9:30 PM, subjects reported to the General Clinical Research Center at St Mary's Hospital, Mayo Clinic. At 10:30 PM subjects received a fourth dose of drug and placebo and then went to sleep. Subjects were awakened for fluorophotometry at 2-hour intervals from 12:00 AM to 6:00 AM for a total of four nighttime measurements. After the 6:00 AM measurement, subjects underwent tonometry with a Goldmann applanation tonometer.

Both times intraocular pressure was measured, the right eye was measured before the left eye, and this procedure was repeated for a total of three measurements of each eye. The intraocular pressure of each eye was recorded as the mean of the three measurements.

The rate of flow was measured by observing the rate of disappearance of topically applied fluorescein from the cornea and anterior chamber. Aqueous flow was calculated with the following equation:

$$\text{Aqueous flow} = \frac{\Delta M_f}{C_a \cdot \Delta t} - \text{diffusional loss}$$

where ΔM_f is the loss of mass of fluorescein in the combined cornea and anterior chamber during an interval

TABLE 1. Sequential and Simultaneous Comparisons of the Effects of Brinzolamide (N = 25)

Variable	Timing of Placebo Measurement	Placebo-Treated Eye (mean ± SD)	Brinzolamide-Treated Eye (mean ± SD)	Percent Difference (mean ± SD) (*P*)
Aqueous humor flow, 8 AM to 4 PM (μl/min)	Simultaneous	2.41 ± 0.38	1.94 ± 0.38	19 ± 10 (<.001)
	Sequential	2.41 ± 0.44	1.94 ± 0.38	19 ± 10 (<.001)
Aqueous humor flow, 12 AM to 6 AM (μl/min)	Simultaneous	0.96 ± 0.18	0.81 ± 0.20	16 ± 14 (<.001)
	Sequential	0.97 ± 0.20	0.81 ± 0.20	16 ± 16 (<.001)
Intraocular pressure at 4 PM (mm Hg)	Simultaneous	15.1 ± 1.7	13.6 ± 1.8	10 ± 7 (<.001)
	Sequential	15.0 ± 2.1	13.6 ± 1.8	8 ± 9 (<.001)
Intraocular pressure at 6 AM (mm Hg)	Simultaneous	10.4 ± 2.0	9.9 ± 2.6	5 ± 19 (.16)
	Sequential	10.0 ± 3.1	9.9 ± 2.6	3 ± 24 (.86)

TABLE 2. Sequential and Simultaneous Comparisons of the Effects of Dorzolamide (N = 25)

Variable	Timing of Placebo Measurement	Placebo-Treated Eye (mean ± SD)	Dorzolamide-Treated Eye (mean ± SD)	Percent Difference (mean ± SD) (*P*)
Aqueous humor flow, 8 AM to 4 PM (μl/min)	Simultaneous	2.32 ± 0.42	2.02 ± 0.39	12 ± 12 (<.001)
	Sequential	2.41 ± 0.44	2.02 ± 0.39	16 ± 11 (<.001)
Aqueous humor flow, 12 AM to 6 AM (μl/min)	Simultaneous	0.97 ± 0.24	0.88 ± 0.20	8 ± 14 (<.01)
	Sequential	0.97 ± 0.20	0.88 ± 0.20	9 ± 16 (<.004)
Intraocular pressure at 4 PM (mm Hg)	Simultaneous	15.0 ± 1.8	13.9 ± 1.9	7 ± 8 (<.001)
	Sequential	15.0 ± 2.1	13.9 ± 1.9	7 ± 8 (<.001)
Intraocular pressure at 6 AM (mm Hg)	Simultaneous	11.0 ± 2.4	9.7 ± 2.5	12 ± 13 (<.001)
	Sequential	10.0 ± 3.1	9.7 ± 2.5	1 ± 19 (<.41)

of time, Δt, and C_a is the average concentration of fluorescein in the anterior chamber during the same time interval, estimated from the initial and final values assuming a single exponential decay. The assumed rate of diffusional loss of fluorescein from the eye is 0.25 μl per min. All fluorophotometric measurements were made with a scanning ocular fluorophotometer as described by McLaren and Brubaker.[22]

Statistical analysis of the data was carried out with a two-tailed, paired Student *t* test to determine significance of differences in flow rates between drug-treated and placebo-treated eyes. A *P* value of less than .05 was considered statistically significant.

In a series of 439 normal human subjects studied, the mean rate of aqueous flow measured in the two eyes simultaneously was 2.80 μl per min. The SD of the signed differences between the left and right eyes of these subjects was 0.45 μl per min, or 16% of the mean. With a sample size of 25 subjects in which one eye serves as the simultaneous control for the other, we should have a 95% chance of detecting an effect of a drug relative to a placebo of 12% or greater.

RESULTS

SIMULTANEOUS COMPARISONS AND SEQUENTIAL COMPARisons are displayed in Tables 1 and 2. Simultaneous comparisons of flows were measured in the drug-treated eye and the placebo-treated fellow eye simultaneously. Sequential comparisons of flows were measured in the same eye but on different days. We compared the drug effects that were found with each method, and with one exception no statistically significant differences were found. This exception was the effect of dorzolamide on intraocular pressure measured simultaneously at 6 AM with placebo vs placebo instilled in the same eye on a different day ($P = .046$). This difference could not have been caused by a contralateral effect, because the intraocular pressure was higher, not lower, in the contralateral eye at the time of the simultaneous test. These results were interpreted as showing that neither drug has a measurable contralateral effect, and consequently we have combined the data from the two methods and made all subsequent comparisons with the combined data (Table 3).

In simultaneous comparisons, brinzolamide reduced the daytime rate of aqueous humor flow from 2.41 ± 0.38 μl per min (mean ± SD) in the placebo-treated eye to 1.94 ± 0.38 μl per min in the brinzolamide-treated eye, a difference of 19% ± 10% ($P < .001$). Brinzolamide also reduced the nighttime rate of aqueous humor flow from 0.96 ± 0.18 μl per min in the placebo-treated eye to 0.81 ± 0.20 μl per min in the brinzolamide-treated eye, a difference of 16% ± 14% ($P < .001$). Brinzolamide reduced the intraocular pressure at 4 PM from 15.1 ± 1.7 mm Hg in the placebo-treated eye to 13.6 ± 1.8 mm Hg in

TABLE 3. Comparison of Effects of Brinzolamide and Dorzolamide (N = 25)

Variable	Brinzolamide-Treated Eye (mean ± SD)	Dorzolamide-Treated Eye (mean ± SD)	*P*
Reduction of aqueous humor flow, 8 AM to 4 PM			
µl/min	0.47 ± 0.20	0.34 ± 0.20	.019
%	19 ± 8	14 ± 9	
Reduction of aqueous humor flow, 12 AM to 6 AM			
µl/min	0.16 ± 0.12	0.10 ± 0.13	.046
%	16 ± 13	8 ± 12	
Reduction of intraocular pressure at 4 PM			
mm Hg	1.5 ± 1.1	1.1 ± 1.0	.17
%	9 ± 6	7 ± 6	
Reduction of intraocular pressure at 6 AM			
mm Hg	0.3 ± 1.6	0.8 ± 1.0	.15
%	1 ± 17	6 ± 10	

the brinzolamide-treated eye, a difference of 10% ± 7% ($P < .001$). Brinzolamide reduced the intraocular pressure at 6 AM from 10.4 ± 2.0 mm Hg in the placebo-treated eye to 9.9 ± 2.6 mm Hg in the brinzolamide-treated eye, a difference of 5% ± 19% ($P = .16$).

Dorzolamide reduced the daytime rate of aqueous humor flow from 2.32 ± 0.42 µl per min in the placebo-treated eye to 2.02 ± 0.39 µl per min in the dorzolamide-treated eye, a difference of 12% ± 12% ($P < .001$). Dorzolamide reduced the nighttime rate of aqueous humor flow from 0.97 ± 0.24 µl per min in the placebo-treated eye to 0.88 ± 0.20 µl per min in the dorzolamide-treated eye, a difference of 8% ± 14% ($P < .01$). Dorzolamide reduced the intraocular pressure at 4 PM from 15.0 ± 1.8 mm Hg in the placebo-treated eye to 13.9 ± 1.9 mm Hg in the dorzolamide-treated eye, a difference of 7% ± 8% ($P < .001$). Dorzolamide reduced the intraocular pressure at 6 AM from 11.0 ± 2.4 mm Hg in the placebo-treated eye to 9.7 ± 2.5 mm Hg in the dorzolamide-treated eye, a difference of 12% ± 13% ($P < .001$).

Table 3 compares the effects of the two drugs. During the day, brinzolamide reduced aqueous flow by 0.47 ± 0.20 µl per min compared with 0.34 ± 0.20 µl per min for dorzolamide ($P = .019$). During the night, brinzolamide reduced aqueous flow by 0.16 ± 0.12 µl per min compared with 0.10 ± 0.13 µl per min with dorzolamide ($P = .046$). Brinzolamide reduced intraocular pressure by 1.5 ± 1.1 mm Hg at the 4 PM measurement compared with a reduction of 1.1 ± 1.0 mm Hg with dorzolamide ($P = .17$). At the 6 AM measurement, brinzolamide reduced intraocular pressure by 0.3 ± 1.6 mm Hg compared with the effect of dorzolamide, 0.8 ± 1.0 mm Hg ($P = .15$).

DISCUSSION

STUDIES HAVE SHOWN THAT DORZOLAMIDE REDUCES aqueous humor flow and intraocular pressure by 18% and 13%, respectively.[8,9] The current findings of reductions of 14% and 7% in a different group of subjects are consistent with the previous studies. In the current study, brinzolamide appears to be slightly more effective in reducing aqueous humor flow than dorzolamide (19% vs 14%). The effect of brinzolamide in the current study is closer to the effect of dorzolamide found in the previous studies. No differences were found in the intraocular pressure effects of the two drugs. We predict that it would be difficult to distinguish the effects of the two drugs in a clinical setting involving patients with glaucoma without studying hundreds of glaucoma patients in a randomized controlled trial. We believe that clinicians who prescribe brinzolamide should expect an ocular hypotensive effect similar to that seen with dorzolamide.

We cannot explain why there was a difference in the results of the statistical test for the effect of dorzolamide on intraocular pressure at the 6 AM measurement when the dorzolamide-treated eye was compared with the simultaneously placebo-treated eye vs the comparison of the dorzolamide-treated eye with the sequentially placebo-treated eye. This finding occurred because the intraocular pressure in the placebo-treated fellow eye during the simultaneous test was higher than that of the other eye at the time of the double placebo measurement. A crossover effect could not have explained this finding, and our opinion is that the finding should be ignored. That opinion is supported by the comparison of the effects of dorzolamide and brinzolamide on the intraocular pressure at 6 AM, where no significant difference was found ($P = .15$). A study of this type, involving normal subjects, in which flow is measured over many hours and intraocular pressure is measured instantaneously, is much more sensitive for discovering differences in effects on aqueous humor flow than it is in discovering differences in effects on intraocular pressure.

Whether these data can be extrapolated to glaucoma patients is a question that is justifiably raised. Three facts support the notion that they can be. First, carbonic anhydrase inhibitors have been shown to reduce intraocular pressure exclusively by reduction of aqueous humor flow. Second, patients with various forms of glaucoma have been reported to have normal aqueous humor flow rates.[23–26] Third, results from other studies of aqueous humor flow in normal subjects with known suppressors have been predictive of the effects in glaucoma patients.[8–10,27–35]

Dorzolamide has been shown to have an additive effect when used with the beta-adrenergic antagonist timolol.[8] These medications are available in combination form, timolol-dorzolamide hydrochloride ophthalmic solution 2% (Cosopt; Merck & Co). It is not yet known whether brinzolamide

is additive to the effects of beta-adrenergic antagonists, and a study to determine if it is would be useful.

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