A Double-Masked, Randomized, 1-Year Study Comparing the Corneal Effects of Dorzolamide, Timolol, and Betaxolol

Jonathan H. Lass, MD; Samer A. Khosrof, MD; Jean K. Laurence, BS; Barry Horwitz, MD; Kalyan Ghosh, PhD; Ingrid Adamsons, MD, MPH; for the Dorzolamide Corneal Effects Study Group

Objective: To compare the long-term effects of dorzolamide hydrochloride (Trusopt, Merck and Co Inc, Whitehouse Station, NJ), timolol maleate, and betaxolol hydrochloride on corneal endothelial cell density and corneal thickness.

Methods: This 1-year multicenter study was conducted in 298 patients with ocular hypertension or open-angle glaucoma who had a baseline central corneal endothelial cell density greater than 1500 cells/mm² and central corneal thickness less than 0.68 mm in each eye. Patients were randomized to 0.5% betaxolol twice daily, 0.5% timolol twice daily, or 2.0% dorzolamide 3 times daily. Specular microscopy and ultrasonic pachymetry of the central cornea was performed at baseline and 6 and 12 months following institution of therapy. Endothelial cell densities were determined by a single masked observer.

Results: The mean percent changes from baseline for both outcome measures were similar in all 3 treatment groups at both 6 and 12 months. After 1 year of treatment, the mean percent loss in endothelial cell density from baseline was 3.6%, 4.5%, and 4.2% for the dorzolamide, timolol, and betaxolol groups, respectively. The mean percent change from baseline for corneal thickness was 0.47%, − 0.25%, and 0.39% for the dorzolamide, timolol, and betaxolol groups, respectively.

Conclusions: Dorzolamide is equivalent to timolol and betaxolol in terms of the change in central endothelial cell density and thickness after 1 year of therapy. All 3 treatments exhibit good long-term corneal tolerability in patients with normal corneas at baseline.


©1998 American Medical Association. All rights reserved.
PATIENTS AND METHODS

This parallel, randomized, double-masked, active-controlled, 1-year study was conducted at 16 sites in the United States. The study was conducted in conformance with applicable requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research. Patients eligible for entry into this study were men or postmenopausal or sterilized women aged 21 years and older with open-angle glaucoma or ocular hypertension. Patients with the following criteria were excluded from study entry: best-corrected visual acuity worse than 20/80 OU; surface epithelial abnormalities such as keratitis sicca; infectious keratitis within 1 year of study entry; imbedded corneal foreign body and/or ocular inflammation within 2 months of study entry; advanced Fuchs dystrophy or any condition that precluded obtaining an analyzable specular microscopic image; contact lens wear within 6 months of study entry; intraocular laser surgery, significant ocular trauma, or intraocular laser therapy within 6 months of study entry; ocular symptoms such as photophobia, metamorphopsia, or diplopia; untreated acute or chronic angle closure; inadequate pupillary dilation for retinal evaluation; and any contraindication to the use of timolol, betaxolol, dorzolamide, or pilocarpine. Other exclusion criteria included: long-term use of medications that could cause dry eyes; concomitant use of systemic carbonic anhydrase inhibitors; previous exposure to dorzolamide longer than 4 weeks; current or previous illicit drug use or chronic alcohol abuse; bronchial asthma or clinically significant chronic obstructive pulmonary disease; sinus bradycardia, second- or third-degree atrioventricular block; uncompensated heart failure, overt cardiac failure, or cardiogenic shock; and participation in any study involving corticosteroids or any condition that precluded obtaining an analyzable specular microscopic image; contact lens wear within 6 months of study entry; intraocular laser surgery, significant ocular trauma, or intraocular laser therapy within 6 months of study entry; ocular symptoms such as photophobia, metamorphopsia, or diplopia; untreated acute or chronic angle closure; inadequate pupillary dilation for retinal evaluation; and any contraindication to the use of timolol, betaxolol, dorzolamide, or pilocarpine. Other exclusion criteria included: long-term use of medications that could cause dry eyes; concomitant use of systemic carbonic anhydrase inhibitors; previous exposure to dorzolamide longer than 4 weeks; current or previous illicit drug use or chronic alcohol abuse; bronchial asthma or clinically significant chronic obstructive pulmonary disease; sinus bradycardia, second- or third-degree atrioventricular block; uncompensated heart failure, overt cardiac failure, or cardiogenic shock; and participation in any study involving administration of an investigational drug within 4 weeks of study entry.

Eligible patients were first required to discontinue all previous topical glaucoma medication and were then treated for 3 weeks with 0.5% betaxolol twice daily in both eyes. At study entry, patients were required to have a baseline IOP of less than 22 mm Hg OU 2 hours after their morning dose of 0.5% betaxolol. In addition, patients were required to have a central corneal endothelial cell density greater than 1500 cells/mm² in each eye and corneal thickness less than 0.68 mm in each eye at the baseline corneal examination within 7 days of study entry.

Patients who met all of the inclusion criteria and who had none of the exclusion criteria were randomized (according to a computer-generated allocation schedule) in 3 groups in a 2:1:1 ratio to receive 2.0% dorzolamide 3 times daily, 0.5% timolol twice daily and placebo once daily, and 0.5% betaxolol twice daily and placebo once daily. Each patient received 2 masked bottles of medication, 1 labeled for 9 AM and bedtime dosing, the other labeled for dosing at 3 PM. For patients assigned to timolol or betaxolol therapy, the 3 PM dosing contained placebo, the vehicle for timolol and betaxolol. Supplementary topical therapy was allowed at or after the month 3 study visit; this was initiated at the discretion of the investigator to maintain adequate IOP control. Patients who were switched to supplementary therapy received 2 new masked bottles of medication: those initially randomized to dorzolamide received 1 bottle containing 2.0% dorzolamide for dosing at 9 AM, 3 PM, and bedtime and 1 bottle containing 0.5% timolol for dosing at 9 AM and bedtime; those initially randomized to timolol or betaxolol received 1 bottle containing the same β-blocker to which they had originally been randomized for dosing at 9 AM and bedtime and 1 bottle containing 2.0% pilocarpine for dosing at 9 AM, 3 PM, and bedtime. In this way, supplementary therapy was double-masked as well. All study drug was packaged by allocation number in identical bottles, which were labeled in blue print for the morning and evening doses and in red for the afternoon doses. When the medication was dispensed, the tear-off label was removed from the bottle and affixed to the patient's case report form. In an emergency, the label could have been swabbed with alcohol to remove the mask and reveal the contents of the bottle. No labels were unmasked during the study. The allocation schedule was kept at Merck Research Laboratories, separate from all persons involved with this study. The database was unmasked only after all data and corrections to the data had been entered into the database and the database had been “frozen.” Thus, no changes could be made to the data following its unmasking.

Prior to study entry, all patients underwent a complete physical examination, blood chemistry and hematology tests, complete ophthalmologic examination including slitlamp biomicroscopy, applanation tonometry, fundus examination, and automated visual field examination. In addition, during the week prior to study entry, the central cornea of patients was examined both with specular microscopy and ultrasonic pachymetry. As specified in the study protocol, at each individual study site, the same specular microscope and the same ultrasonic pachymeter were used for all patient measurements. All study sites used contact specular microscopes. Each ultrasonic pachymeter was calibrated for the same acoustic velocity in the cornea.

RESULTS

Two hundred ninety-eight patients with a mean age of 60.8 years were enrolled in the study: 148 in the dorzolamide group, 72 in the timolol group, and 78 in the betaxolol group (Table 1). The patients were predominantly white (82%) with slightly more women (54%) than men. The 3 groups did not differ for age, sex, or race. Similar distributions were also observed among the treatment groups for baseline endothelial cell density, corneal thickness, and IOP. Approximately 40% of patients in each treatment group had been diagnosed with ocu-
Following ultrasonic pachymetry of the central cornea, specular microscopy was performed in the same area. All 35-mm negatives or video images of the central corneal endothelium for all clinical sites were analyzed at the Endothelial Image Analysis Reading Center (University Hospitals of Cleveland, Cleveland, Ohio) by a single trained, masked technician for the entire study, using a video enhancement digitization system (BioOptics, Arlington, Mass). Images were calibrated from each site using an image of a micrometer slide (American Scientific Products, Minneapolis, Minn) or calibration contact lens (BioOptics) obtained at the same magnification as the clinical images from each specular microscope. Central endothelial cell density was determined by a modified method of fixed-frame analysis of endothelial cells within a rectangle of a varying known area for each image based on its magnification. The rectangle was created by the technician with the calibrated image to count a clear image of between 50 and 100 cells within the known area of the rectangle. Partial cells were counted along one contiguous horizontal and vertical border of the rectangle. The Reading Center informed the Merck study monitor whether the image was analyzable, whether the cell density was greater than 1500 cells/mm², and provided the cell density for each subject to the study monitor, who assigned the patient allocation number to 1 of 2 subgroups within each treatment group according to the stratification of the cell density (1500-2200 cells/mm² or >2200 cells/mm²). No patient was allowed to enter the study unless the baseline examinations were satisfactorily completed.

The baseline study examination included best-corrected visual acuity, external and slitlamp biomicroscopy, and application tonometry performed approximately 2 hours after the morning dose of betaxolol. Similar examinations, including application tonometry approximately 2 hours after the morning dose of study medication, were performed at study week 2 and months 3, 6, 9, and 12. Central ultrasonic pachymetry followed by central specular microscopy was performed at study months 6 and 12. If supplementary therapy was initiated, central ultrasonic pachymetry followed by central specular microscopy was performed at that study visit, prior to the initiation of the supplementary therapy. Hematology and blood chemistry tests were performed on the day the patient completed or discontinued the study, and within 5 days of completing or discontinuing the study the following were performed: physical examination, best-corrected visual acuity measurement, dilated ophthalmoscopy, and automated visual field examination.

Corneal effects were assessed using the percent change from baseline in central corneal endothelial cell density and corneal thickness. The percent changes for both eyes were averaged to obtain a single value for each patient at each visit. Four approaches were used to analyze these data: (1) All patients treated, last observation carried forward, which was the primary analysis; (2) all patients treated, month 12 data only; (3) monotherapy data only, last observation carried forward; and (4) monotherapy data only, month 12 data only. Because all 4 analyses provided similar results, only the results from the primary analysis will be presented in this report.

The primary study hypothesis was that dorzolamide is equivalent to both timolol and betaxolol in terms of percent change from baseline in central endothelial cell density and corneal thickness. Two agents were considered equivalent if the confidence level was 0.95 ± 0.10. These ranges were chosen while designing the study by consultation with several corneal specialists and by the literature. This study had more than 95% power of concluding equivalence if the response to the 3 treatments was indeed equal, assuming a standard deviation of 1.2% for endothelial cell loss and 3% for the change in corneal thickness. Treatment group comparisons were made using analysis of variance (ANOVA) techniques. Age at study entry, baseline corneal endothelial cell density, baseline corneal thickness, and baseline IOP were compared among the treatment groups using a 2-way ANOVA model with investigator and treatment as main effects and no interaction. Summary statistics were calculated for corneal endothelial cell density and corneal thickness for each of the following baseline covariates: investigator, age (<65 years vs ≥65 years), race (white vs other), sex, and iris color (dark vs light).

Treatment group comparisons with regard to the following binary variables were made using the Fisher exact test (2-tailed): patient characteristics (race and sex), secondary diagnoses, prior and concomitant therapies, incidence of clinical and laboratory adverse experiences, incidence of emerging or worsening ocular signs, incidence of doubling of visual angle, and incidence of “significant clinical progression” (as determined by the investigator) of visual field defects from baseline. Statistical significance was declared if the rounded P was .05 or less. All analyses were performed using SAS software, version 6.10 (SAS Institute, Cary, NC).

Intracoroidal pressure was evaluated using data from the worse eye. The worse eye was defined as the eye with the higher IOP at hour 2 at baseline. If both eyes were equal at that time, then the right eye was selected. Change and percent change from baseline IOP were summarized by treatment group for each study visit.

Table 2 and Figure 1 present the summary statistics for changes in central corneal endothelial cell density during the 1-year study period. The mean percent endothelial cell loss was similar in all 3 treatment groups at both 6 and 12 months. At 12 months, the mean endothelial
cell loss was 3.6%, 4.5%, and 4.2% for the dorzolamide, timolol, and betaxolol groups, respectively. At both 6 and 12 months, in our study sample, the dorzolamide group had the smallest absolute and percent changes from baseline. At 12 months, the mean difference in percent change between dorzolamide and timolol was 0.72% with a 95% confidence interval (CI) of −0.54% to 1.97%. The mean difference between dorzolamide and betaxolol at 12 months was 0.48%, with a 95% CI of −0.74% to 1.70%. There was more than 99.9% confidence that the mean difference in percent change from baseline in endothelial cell density between dorzolamide and timolol and between dorzolamide and betaxolol was within −10% and 10%. Based on the definition of equivalence in the protocol (>95% confidence), the 3 treatment groups were demonstrated to be equivalent in terms of change in corneal endothelial cell density from baseline.

The effects of various covariates on the percent change in central corneal endothelial cell density were evaluated. There was a significant effect of investigator (P < .001); in other words, the percent change in central corneal endothelial cell density varied significantly from study site to study site. There also was a significant effect of age (P < .05) and iris color (P < .01) (Table 3). Patients younger than 65 years had less cell loss than did patients older than 65 years, and patients with dark irides had less cell loss than did patients with light irides. There was no significant effect of any of the other covariates on percent endothelial cell loss.

Table 4 and Figure 2 present the summary statistics for central corneal thickness. The mean percent

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Patients</th>
<th>Baseline</th>
<th>Treatment</th>
<th>Change From Baseline</th>
<th>Percent Change From Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dorzolamide hydrochloride</td>
<td>140</td>
<td>2400 (342)</td>
<td>2359 (341)</td>
<td>−42 (112)</td>
<td>−1.6 (4.8)</td>
</tr>
<tr>
<td>Timolol maleate</td>
<td>68</td>
<td>2394 (343)</td>
<td>2332 (344)</td>
<td>−61 (98)</td>
<td>−2.5 (4.0)</td>
</tr>
<tr>
<td>Betaxolol hydrochloride</td>
<td>72</td>
<td>2438 (412)</td>
<td>2385 (399)</td>
<td>−53 (57)</td>
<td>−2.1 (2.3)</td>
</tr>
<tr>
<td>12 mo</td>
<td></td>
<td>2407 (351)</td>
<td>2317 (346)</td>
<td>−90 (123)</td>
<td>−3.6 (5.0)</td>
</tr>
<tr>
<td>Dorzolamide</td>
<td>141</td>
<td>2405 (353)</td>
<td>2295 (340)</td>
<td>−110 (106)</td>
<td>−4.5 (4.2)</td>
</tr>
<tr>
<td>Timolol</td>
<td>69</td>
<td>2462 (428)</td>
<td>2358 (415)</td>
<td>−105 (89)</td>
<td>−4.2 (3.6)</td>
</tr>
</tbody>
</table>

*Data are given as mean (SD) unless otherwise indicated.

### Table 1. Patient Demographics*

<table>
<thead>
<tr>
<th></th>
<th>Dorzolamide hydrochloride (n = 148)</th>
<th>Timolol maleate (n = 72)</th>
<th>Betaxolol hydrochloride (n = 78)</th>
<th>Total (N = 298)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>Mean ± SD</td>
<td></td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>62.1 ± 12.5</td>
<td>63.2 ± 11.1</td>
<td>58.7 ± 13.1</td>
<td>60.8 ± 12.4</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>71 (48)</td>
<td>26 (36)</td>
<td>41 (53)</td>
</tr>
<tr>
<td>Female</td>
<td>77 (52)</td>
<td></td>
<td>46 (64)</td>
<td>37 (47)</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
<td>117 (79)</td>
<td>61 (85)</td>
<td>66 (85)</td>
</tr>
<tr>
<td>Black</td>
<td>28 (19)</td>
<td></td>
<td>9 (12)</td>
<td>12 (15)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (2)</td>
<td></td>
<td>2 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Baseline corneal endothelial cell density, cells/mm²</td>
<td>Mean ± SD</td>
<td>2422 ± 351</td>
<td>2401 ± 357</td>
<td>2461 ± 424</td>
</tr>
<tr>
<td>Range</td>
<td>1628-3560</td>
<td>1588-3156</td>
<td>1508-3624</td>
<td>1508-3629</td>
</tr>
<tr>
<td>Baseline corneal thickness, mm</td>
<td>Mean ± SD</td>
<td>0.583 ± 0.038</td>
<td>0.560 ± 0.034</td>
<td>0.569 ± 0.035</td>
</tr>
<tr>
<td>Range</td>
<td>0.469-0.665</td>
<td>0.483-0.642</td>
<td>0.447-0.639</td>
<td>0.447-0.665</td>
</tr>
<tr>
<td>Baseline intraocular pressure, mm Hg</td>
<td>Mean ± SD</td>
<td>18.8 ± 2.2</td>
<td>18.9 ± 2.0</td>
<td>18.7 ± 2.1</td>
</tr>
<tr>
<td>Range</td>
<td>10-22</td>
<td>13-22</td>
<td>13-21</td>
<td>10-22</td>
</tr>
<tr>
<td>Primary diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular hypertension</td>
<td>58 (39.2)</td>
<td>30 (41.7)</td>
<td>29 (37.2)</td>
<td>117 (39.3)</td>
</tr>
<tr>
<td>Primary open-angle glaucoma</td>
<td>85 (57.4)</td>
<td>39 (54.2)</td>
<td>48 (61.5)</td>
<td>172 (57.7)</td>
</tr>
<tr>
<td>Pseudoexfoliative glaucoma</td>
<td>2 (1.4)</td>
<td>2 (2.8)</td>
<td>0 (0.0)</td>
<td>4 (1.3)</td>
</tr>
<tr>
<td>Pigmentary glaucoma</td>
<td>6 (4.1)</td>
<td>3 (4.2)</td>
<td>2 (2.6)</td>
<td>11 (3.7)</td>
</tr>
</tbody>
</table>

*All data are given as number (percentage) unless otherwise specified. Seventy-seven patients receiving betaxolol contributed intraocular pressure data. Some patients had more than one primary diagnosis.
change in corneal thickness was similar in all 3 treatment groups at both 6 and 12 months. At 12 months, the mean percent change in corneal thickness from baseline was an increase of 0.47% and 0.39% for the dorzolamide and betaxolol groups, respectively, and a decrease of 0.25% for the timolol group. At 12 months, the mean difference between dorzolamide and timolol was 0.79% with a 95% CI of 0.07 to 1.51. The mean difference between dorzolamide and betaxolol at 12 months was 0.08% with a 95% CI of −0.62 to 0.79. There was more than 99.9% confidence that the mean difference in percent change from baseline in corneal thickness between dorzolamide and timolol was −10% and 10%. Based on this definition of equivalence, the 3 treatment groups were demonstrated to be equivalent in terms of change in central corneal thickness from baseline. The effects of various covariates on the percent change in corneal thickness were also evaluated; investigator was the only significant factor (P < .01).

Slitlamp evaluation of the cornea was performed at each study visit and the data were evaluated for any emergent or worsening corneal signs reported at any study visit. Corneal signs were reported by 11 patients (8%) in the dorzolamide group, 6 patients (9%) in the timolol group, and 8 patients (10%) in the betaxolol group. The most commonly reported sign in the dorzolamide group was arcus senilis (3 patients [2%]); punctate corneal erosions were the most commonly reported sign in the other 2 groups (6 patients [9%] in the timolol group and 8 patients [10%] in the betaxolol group). The only statistically significant difference among the 3 treatment groups was in the incidence of punctate corneal erosion between the dorzolamide and timolol groups (1 patient [1%] vs 6 patients [9%], respectively; P = .005).

**ADVERSE EVENTS**

The most frequently reported adverse experiences were ocular burning and/or stinging (22% in the dorzolamide group, 14% in the timolol group, and 24% in the betaxolol group), conjunctival injection (12% in the dorzolamide group, 11% in the timolol group, and 5% in the betaxolol group), and headache (3% in the dorzolamide group, 12% in the timolol group, and 10% in the betaxolol group). The only statistically significant difference among the groups with regard to these adverse experiences was for headache: a smaller proportion of patients receiving dorzolamide reported headache than those receiving timolol or betaxolol (3% vs 12%, P = .01; 3% vs 10%, P = .03, respectively). However, the proportion of patients reporting taste perversion was higher in the dorzolamide group than in either the timolol group (13% vs 0%, P = .001) or the betaxolol group (13% vs 0%, P < .001).

Twenty-one patients discontinued the study because of a clinical adverse experience: 12 patients (8%) receiving dorzolamide, 3 patients (4%) receiving timolol, and 6 patients (8%) receiving betaxolol. Eight of the 12 patients who discontinued dorzolamide had drug-related adverse experiences. Of these 8 patients, 5 patients had drug-related ocular adverse experiences: conjunctivitis, eyelid dermatitis, conjunctival injection, and eyelid irritation. The remaining 3 patients had drug-related ocular adverse experiences: conjunctivitis, eyelid dermatitis, conjunctival injection, and eyelid irritation. The remaining 3 patients had drug-related ocular adverse experiences: conjunctivitis, eyelid dermatitis, conjunctival injection, and eyelid irritation.
related nonocular adverse experiences: sinus disorder, headache, paresthesia, and asthenia and/or fatigue.

**INTRAOCULAR PRESSURE**

The change and percent change in IOP from baseline (ie, at the end of the betaxolol run-in period) are presented for each of the 3 treatment groups in Table 5. The mean change in IOP from the end of the betaxolol baseline to month 12 was less than 1 mm Hg for all 3 treatments.

**COMMENT**

Dorzolamide is a potent inhibitor of CA-II, which is found in several locations in the eye, including the corneal endothelium. shutter stock.

Concern has therefore been expressed that the drug may exert an adverse effect on corneal endothelial cells by inhibiting the bicarbonate pump. Evidence that mitigates against this concern includes preclinical studies in which no statistically or clinically significant changes in corneal thickness were observed in animals receiving dorzolamide in concentrations of up to 4% for up to 3 months. 

The short-term corneal effects of dorzolamide have also been demonstrated in a 4-week clinical study in which no clinically meaningful changes in either corneal thickness or corneal endothelial cell density were measured. Timolol and betaxolol are 2 ocular hypotensive agents whose mechanism of action does not pose a specific risk to corneal endothelial cells. These agents have also not been associated with corneal endothelial decompensation in clinical use, despite long-term, widespread use. This 1-year clinical study has shown that topical therapy with dorzolamide exerts an equivalent effect on corneal thickness or corneal endothelial cell density as betaxolol or timolol in patients with clinically normal corneas (ie, central corneal endothelial cell density >1500 cells/mm² and central corneal thickness <0.68 mm).

Corneal endothelial cell function can be assessed by various measures. Because of its ease and rapidity of measurement, corneal thickness is most suitable for large-scale clinical studies. However, this measurement is limited because it is an indirect measure that is influenced not only by endothelial cell function, but also by the status of the epithelial and endothelial barriers, stromal inhibition pressure, and IOP. Other in vivo measures that more directly measure endothelial function include endothelial morphometry, fluorophotometric measurement of endothelial permeability and pump function, and de-swelling rate after induced hypoxia. Unfortunately, these techniques are too time consuming, and consequently impractical, to have been used in this large clinical study. However, other investigators have used these techniques to examine the effect of dorzolamide in normal subjects and in patients with open-angle glaucoma or ocular hypertension and found no short-term effects on endothelial permeability and de-swelling rate. Therefore, while we were able to assess overall corneal hydration based on corneal thickness (measured ultrasonically), the long-term effects of these 3 therapies on endothelial pumping function were not determined with these more specific techniques.

The determination of central endothelial cell density cannot directly relate to endothelial function because of the significant functional reserve of this cell layer. However, once the central endothelial cell density drops below 300 to 500 cells/mm², the remaining endothelial cells can no longer adequately dehydrate the stroma and generally the cornea will begin to swell clinically and by pachymetry. Central corneal endothelial cell density and cell loss was therefore studied, because it is eas-

---

**Table 4. Central Corneal Thickness by Treatment**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of Patients</th>
<th>Corneal Thickness, mm</th>
<th>Change From Baseline</th>
<th>Percent Change From Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Treatment</td>
<td>From Baseline</td>
<td>From Baseline</td>
</tr>
<tr>
<td>Dorzolamide hydrochloride</td>
<td>139</td>
<td>0.562 (0.036)</td>
<td>0.564 (0.036)</td>
<td>0.001 (0.013)</td>
</tr>
<tr>
<td>Timolol maleate</td>
<td>69</td>
<td>0.559 (0.034)</td>
<td>0.558 (0.037)</td>
<td>0.002 (0.015)</td>
</tr>
<tr>
<td>Betaxolol hydrochloride</td>
<td>74</td>
<td>0.569 (0.034)</td>
<td>0.572 (0.034)</td>
<td>0.003 (0.012)</td>
</tr>
<tr>
<td></td>
<td>140</td>
<td>0.561 (0.036)</td>
<td>0.564 (0.036)</td>
<td>0.002 (0.012)</td>
</tr>
<tr>
<td>Timolol</td>
<td>69</td>
<td>0.559 (0.034)</td>
<td>0.558 (0.036)</td>
<td>0.002 (0.018)</td>
</tr>
<tr>
<td>Betaxolol</td>
<td>75</td>
<td>0.568 (0.034)</td>
<td>0.571 (0.035)</td>
<td>0.002 (0.014)</td>
</tr>
</tbody>
</table>

* Data are given as mean (SD) unless otherwise indicated.
than 65 years had less cell loss than did patients older and iris color on endothelial cell loss: patients younger and patients with dark irides had less cell loss than did patients with light irides. While the significance of iris color findings may not be clear, the difference in cell loss depending on age suggests that older endothelium may be more subject to cell loss. This difference was not clinically significant in our study, with only 1 percentage point difference between the 2 age groups. However, it is possible that an older endothelial cell population will have greater cell loss when stressed. For example, in a study of endothelial cell loss 1 year after penetrating keratoplasty, recipients of grafts from older donors (>50 years) showed greater percent cell loss (mean, 27.1%) than recipients of grafts from young donors (<25 years) (mean, 16.5%). Another study found consistent results at 1 year after penetrating keratoplasty but this effect was not observed at 3 or 5 years after the surgery. Greater cell loss following penetrating keratoplasty has also been observed in donor eyes with higher baseline cell density. For this reason, the 3 groups in this study were stratified by baseline cell density of 1500 to 2200 cells/mm² or greater than 2200 cells/mm². No difference in cell loss, however, was noted in our study based on baseline cell density.

During this study, the cornea was also evaluated by slitlamp biomicroscopy at each study visit. The 3 treatment groups were very similar in terms of emergent or worsening corneal signs. The only statistically significant difference was between the dorzolamide and timolol groups in the percentage of patients with punctate corneal erosions. It is not clear why this difference occurred; however, all 7 cases were reported as being mild in severity. Thus the clinical significance of this finding may be limited.

The 3 treatment groups also differed in the frequency with which taste perversion and headache were reported. Taste perversion was reported significantly more frequently with dorzolamide than with either of the 2 β-blockers; this finding has been previously reported. In contrast, headaches were reported significantly less frequently with dorzolamide than with either timolol or betaxolol. In another 1-year study comparing the same 3 therapies, headache was reported significantly less frequently in patients receiving dorzolamide or timolol than in patients receiving betaxolol (5% vs 12%, P = .01; 2% vs 12%, P = .006, respectively).
In conclusion, this study found that the effects of dorzolamide, timolol, and betaxolol on the cornea were quite similar. It is worth emphasizing that glaucoma patients were eligible for this study only if their corneas were clinically normal. Thus, these study findings may not be generalizable to patients with compromised corneas. Indeed, there have been reports of corneal decompensation in patients with severely compromised corneas who were treated with dorzolamide. Nonetheless, the results of this study provide information that may be valuable to the majority of glaucoma patients.

Accepted for publication May 1, 1998.

This study was supported by Merck and Co Inc, Whitehouse Station, NJ, and in part by the Ohio Lions Eye Research Foundation, Cleveland, and Research to Prevent Blindness Inc, New York, NY.

We wish to thank Gina Diaconu for technical assistance.

Reprints: Ingrid Adamsons, MD, MPH, Merck Research Laboratories, 10 Sentry Pkwy, BL1-3, Blue Bell, PA 19422.

REFERENCES