Effect of Dorzolamide on Corneal Endothelial Function in Normal Human Eyes

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PURPOSE. To assess the effects of dorzolamide hydrochloride, a topical carbonic anhydrase inhibitor, on corneal endothelial function.

METHODS. The authors measured the rate of corneal deswelling and the endothelial permeability to fluorescein after 2 hours of hypoxic contact lens wear in 19 normal human subjects. The study was double-masked; one eye of each subject was randomly assigned to receive 2% dorzolamide drops, and the other eye received placebo drops every 8 hours for 24 hours before the study day and twice during the study day.

RESULTS. Dorzolamide-treated eyes were not significantly different from placebo-treated eyes in corneal deswelling rate, expressed as the percent recovery per hour (55.7% ± 13.6% versus 59.6% ± 14.5%, P ≥ 0.10), open eye steady state thickness, swelling induced by hypoxia, and corneal autofluorescence. Endothelial permeability to fluorescein was increased in the dorzolamide eyes (4.40 ± 0.84 × 10^-4 cm/minute versus 4.10 ± 0.80 × 10^-4 cm/minute; P = 0.01). As expected, the intraocular pressure and aqueous humor flow rate were decreased in the dorzolamide eyes.

CONCLUSIONS. Dorzolamide hydrochloride, when topically administered to normal human eyes for 24 hours, had no significant effect on the corneal deswelling rate after hypoxic stress. The corneal endothelial permeability to fluorescein, however, was increased by the drug, although this did not result in increased corneal thickness. (Invest Ophthalmol Vis Sci. 1998;39:23-29)

Dorzolamide, a carbonic anhydrase (CA) inhibitor administered topically, has recently been approved as a treatment for glaucoma. By inhibiting the CA-dependent step of aqueous humor secretion by the ciliary body, the drug suppresses aqueous humor production, thereby decreasing intraocular pressure. In addition to the nonpigmented ciliary epithelial cells that secrete aqueous humor, the corneal endothelial cells also have CA activity in their plasma membranes and cytoplasm. A topical CA inhibitor should affect corneal endothelial CA activity and possibly compromise endothelial function. The corneal endothelium maintains corneal transparency by pumping fluid from the corneal stroma. This energy-dependent process can be inhibited in vitro by specific inhibitors of CA, such as acetazolamide. In vivo, however, acetazolamide is given systemically to patients with no apparent ill effects on corneal function in normal eyes.

Studies of the side effects of dorzolamide in animals show that the drug is tolerated well with no changes in corneal thickness and normal biomicroscopic and histologic examinations. In humans, a small statistically significant increase in mean corneal thickness was found in a 4-week safety and efficacy study of dorzolamide, but it was not clinically significant. Of concern to clinicians, however, are reports of four cases of irreversible corneal decompensation after using dorzolamide to treat patients with corneal transplants that had borderline corneal endothelial function.

Endothelial cells play an important role in recovering normal corneal thickness after the cornea is decompensated by stresses such as surgery or contact lens wear, and knowing the effect of ophthalmic medications on the ability of corneas to recover after a transient insult is important. In this study we investigated the effect of dorzolamide on corneal recovery after a known, reversible stress: short-term hypoxia induced by a contact lens.

MATERIALS AND METHODS

Subjects

Nineteen normal human subjects selected from patients and employees of the Mayo Clinic gave informed written consent to participate in this protocol, which followed the dictates of the Declaration of Helsinki and was approved by the Institutional Review Board at the Mayo Clinic. Subjects were between 20 and 52 years old and were found to be normal upon ophthalmic examination, including visual acuity, slit lamp examination, applanation tonometry, and nondilated fundus examination. The subjects' corrected visual acuities were better than 20/40, and their intraocular pressures, less than 22 mm Hg, were symmetrical within 3 mm Hg. None of the subjects had diabetes mellitus or any serious chronic disease, were pregnant or breast feeding, or had recently used any systemic or ocular medications other than acetaminophen. Subjects were excluded if they had a history of contact lens wear, keratoconjunctivitis sicca, cornea guttata, recent ocular infections, ocular inflammation, eye surgery, eye trauma, ocular laser treatment, or a family history of eye disease other than cataract after age 50. During the afternoon of the baseline
examination, the corneal endothelium was photographed with a wide-field contact specular microscope, and the corneal autofluorescence was measured at 488-nm and 457.9-nm wavelengths using a scanning ocular fluorophotometer.\textsuperscript{14}

Two dropper bottles were prepared for each subject, one with dorzolamide hydrochloride 2% (Trusopt; Merck, West Point, PA) and the other with a placebo (Isopo-Plain; Alcon, Fort Worth, TX). The composition of the carrier was not identical with that of the available placebo: 2% dorzolamide had a pH of 5.6 and a benzalkonium chloride concentration of 0.0075%, and the placebo had a pH buffered between 6.0 and 7.8 and a benzalkonium chloride concentration of 0.01%. A double-masked randomized protocol was prepared by the hospital pharmacy. Each drug application was randomly applied to the left or right eye, and half of the subjects received drug in the right eye and half in the left. The other eye received the placebo. The investigator was not told which eye received the drug. One drop from each bottle was instilled in the appropriate eye at 8 AM, noon, and 5 PM on the day before the study and at 8 AM and noon on the day of the study. Subjects were told that either the drug or the placebo could cause discomfort and were instructed not to tell the investigator about stinging until after the intraocular pressures had been recorded at the end of the day. After all subjects had completed the protocol, the remaining solution in each of the dropper bottles was analyzed by absorption spectroscopy to determine which bottles contained the drug; the randomization code used by the hospital pharmacy was confirmed in each case.

The protocol for the study day was similar to previous corneal hydration control studies\textsuperscript{5-7} with minor modifications. At 2 AM on the study day, subjects instilled 3 to 5 drops of 2% fluorescein (Iolab, Claremont, CA) in each eye according to age—5 drops if younger than 27 years old, 4 drops if 27 to 35 years old, and 3 drops if older than 35 years—and then resumed sleep. At 8 AM, corneal thickness and corneal and anterior chamber fluorescence were measured. An aphakic hydrogel contact lens (38% water content, +20.00 diopters, 7.8 and a benzalkonium chloride concentration of 0.0075%, and the placebo had a pH buffered between 6.0 and 7.8 and a benzalkonium chloride concentration of 0.01%). A double-masked randomized protocol was prepared by the hospital pharmacy. Each drug application was randomly applied to the left or right eye, and half of the subjects received drug in the right eye and half in the left. The other eye received the placebo. The investigator was not told which eye received the drug. One drop from each bottle was instilled in the appropriate eye at 8 AM, noon, and 5 PM on the day before the study and at 8 AM and noon on the day of the study. Subjects were told that either the drug or the placebo could cause discomfort and were instructed not to tell the investigator about stinging until after the intraocular pressures had been recorded at the end of the day. After all subjects had completed the protocol, the remaining solution in each of the dropper bottles was analyzed by absorption spectroscopy to determine which bottles contained the drug; the randomization code used by the hospital pharmacy was confirmed in each case.

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Six subjects had been involved in another earlier 2-day study to compare the effects of acetazolamide and dorzolamide on aqueous flow.\textsuperscript{1} With these subjects, we compared endothelial permeability in the earlier study, under normal steady-state conditions, to permeability in the present study, in which swollen corneas are deswelling under normoxic conditions. In the earlier study, eye drops were administered at the same time of day as in the present study. For the six subjects in both studies, we used the previous randomization schedule so that the same eye received drug in both studies. In the previous study, subjects also received either acetazolamide or a placebo systemically on each day in a randomized order. Permeability of the unswollen cornea in steady state was calculated from corneal and cameral fluorescence at noon, 2:00 PM, and 4:00 PM in placebo eyes on days when acetazolamide was not given. Contact lenses were not worn in this previous study, and the corneal thickness was not measured. We assumed that the corneal thickness was constant for each subject and equal to the open eye steady state (OESS) thickness measured for that subject in the present study.

**Instrumentation and Analysis**

**Pachometry.** Puleo and co-workers\textsuperscript{18} have shown that deswelling to the OESS thickness resembles a first-order process; the deswelling rate is described by:

\[
q(t) = B + S e^{-Dt}
\]

where \(q(t)\) is the measured corneal thickness at time \(t\); \(B\) is the OESS thickness, \(S\) is the initial corneal thickness in excess of \(B\) (corneal swelling) when the contact lens is removed, and \(D\) is the deswelling rate constant. For each experiment, we determined \(B\), \(S\), and \(D\) by using a nonlinear regression technique (S-PLUS; Statistical Systems, Seattle, WA) from corneal thicknesses measured between 1 and 6.5 hours after contact lens removal. Corneal thickness measurements from the first 50 minutes after contact lens removal were excluded from the analysis because stromal pH is decreased during this period,\textsuperscript{19} and decreased pH reduces the deswelling rate.\textsuperscript{20} Deswelling was expressed as a clinically meaningful parameter, percent recovery per hour (PRPH):

\[
PRPH = (1 - e^{-60D}) \times 100
\]

We measured central corneal thickness by using a Haag-Streit optical pachometer, modified with fixation lights, and a direct electronic recording system as described by Mandell et al.\textsuperscript{21} The mean of 10 consecutive measurements with the pachometer was recorded as corneal thickness. One examiner (CAE) measured all corneal thicknesses and did not know the value recorded until all 10 were completed. If the standard deviation of the 10 values exceeded 10 μm, the measurements were repeated. Each morning, the examiner calibrated the pachometer to a set of contact lenses of known thickness. To avoid errors in calibration that result from the use of different endpoints for the calibration lenses than for the in vivo corneas, a constant correction factor was added for each cornea based on its thickness measured by the specular microscope during the afternoon of the baseline examination.

**Endothelial Permeability.** Endothelial permeability to fluorescein was calculated for each interval according to the following relationship,\textsuperscript{22} based on the method of Jones and Maurer\textsuperscript{23}:

\[
perm = \frac{q(t_a)[C_e(t_1) - C_e(t_0)]}{[r_a(C_e(t_1) - C_e(t_0))(t_1 - t_0)]}
\]

where \(perm\) is permeability, \(q\), is the mean cornea thickness on the interval, \(t_0\) and \(t_1\) are time at the beginning and end of the interval, \(C_e(t)\) is the concentration of fluorescein in the cornea at time \(t\), \(r_a\) is the ratio of concentration of fluorescein in the cornea to that in the anterior chamber when they are in equilibrium (assumed to be 1.6 in corneas at normal thickness\textsuperscript{24}), and \(C_e\) and \(C_a\) are the mean concentrations of fluorescein in the cornea and anterior chamber on the interval. When
concentrations decrease logarithmically, as they did here, a simple arithmetic mean overestimates the average concentration on the interval, and a better estimate is given by

\[
\tilde{C} = \frac{C_0 - C_1}{\ln(C_0/C_1)}
\]

where \(C_0\) and \(C_1\) are concentrations at the beginning and the end of the interval. Equation 4 was used to determine \(\tilde{C}\) and \(\tilde{C}_e\).

The distribution ratio \(r_{ca}\) is used in equation 3 to account for fluorescein bound to protein in the cornea. When the cornea swells, fluorescein binding sites are diluted in proportion to the change in volume, or thickness. The value of \(r_{ca}\) that was used in equation 3 was adjusted to account for the reduced binding by using:

\[
r_{ca} = \frac{q_s}{q} (r_{ca}-1) + 1
\]

where \(q\) is the actual thickness of the cornea, and \(q_s\) is the value of \(r_{ca}\) in human corneas of normal thickness \(q_o\), and was assumed to be 1.6. We used the thickness measured at 8:00 AM as the value for \(q_o\) for each subject.

Fluorescence in the anterior chamber and cornea was measured by using a two-dimensional scanning ocular fluorophotometer. When this instrument measures fluorescence in a thin structure such as the cornea, the measurement is influenced by cornea thickness because the focal diamond extends slightly beyond the anterior and posterior surfaces of the cornea. This underestimate can be corrected by multiplying the measured fluorescence by a factor based on cornea thickness. The relation between the correction factor and thickness was determined by measuring fluorescence of a fluorescein solution in a variable-thickness chamber constructed from two contact lenses, as described by Taarnhøj et al. The correction factor, the ratio between fluorescence measured in a solution of 2-mm depth to fluorescence of the same solution at the thickness of the cornea, was approximately linear for thickness between 500 \(\mu\)m and 700 \(\mu\)m. Because cornea thickness was intentionally made to change during this study, corneal fluorescence was multiplied by a correction factor based on the thickness measured within 15 minutes of the fluorescence measurement.

We determined permeability over two intervals. The first, termed the AM permeability, was calculated from fluorescence measured at approximately 8:00 AM and 11:30 AM, before contact lens insertion and 1 hour after its removal. We did not use fluorescence during the initial 50 minutes after contact lens removal because stromal pH is decreased during this period, and decreased pH reduces the fluorescence efficiency of fluorescein. The second interval, termed the PM permeability, was calculated from fluorescence measured hourly from noon until 5:00 PM. In the afternoon, corneal fluorescence decreased logarithmically. We attempted to reduce the sensitivity of the PM permeability calculation to errors in measuring \(C_0\) by fitting \(\log(C_0)\) and time to a line. We then used points on the line in place of \(C_0(t)\) in equation 3.

For comparison, we also calculated endothelial permeability from the fluorescence data of all 20 subjects in the previous study by the standard method, assuming that the cornea was not swollen. A corneal thickness of 0.5 mm was assumed for all subjects.

**Corneal Endothelial Specular Microscopy.** During the baseline examination of each subject, corneal endothelium was photographed 5 to 10 times and central corneal thickness was measured with a wide-field contact specular microscope. The photographic negatives were recorded with a video camera, and the apices of 100 cells were digitized from the video image. The mean and standard deviation of cell area and the percentage of cells with six sides were computed by using a commercial algorithm (Bambi system; Bio-Optics, Bedford, MA). We also measured the anterior chamber volume of each eye by using a photogrammetric method.

**Statistical Analysis.** We compared treated eyes with untreated eyes by using a paired \(t\)-test when the data were distributed normally and a Wilcoxon signed-rank test when they were not. Correlations between continuous variables were made with Pearson's correlation coefficient for normally distributed data and Spearman's rank correlation coefficient for data that were not distributed normally. A two-tailed probability of 0.05 or less was considered statistically significant.

**RESULTS**

Corneal deswelling was not significantly affected by dorzolamide treatment (Table 1 and Fig 1). Several subjects had substantially lower PRPH in the dorzolamide-treated eye, but these eyes did not differ significantly from their mates or from the other eyes in the group concerning any of the morphologic or functional measurements. Treatment with dorzolamide decreased intraocular pressure and aqueous humor flow rate and increased PM endothelial permeability (Fig. 2). The baseline endothelial cell density was significantly less in the eyes randomized to dorzolamide treatment. All other parameters in drug-treated eyes were not significantly different from those in placebo-treated eyes. There were no statistically significant correlations between endothelial cell density and PRPH, OESS thickness, or induced swelling in either the drug-treated or placebo-treated eyes. Endothelial cell density and PM permeability were significantly correlated in the placebo-treated eyes \((r = 0.59; P = 0.008)\), but not in the drug-treated eyes.

The PM permeability data for the six subjects who were involved in the previous study are listed in Table 2. Results obtained in both studies were not significantly different for these six subjects.

The endothelial permeability results from all 20 subjects in the previous study are presented in Table 3. The results show a statistically significant increase in endothelial permeability to fluorescein in the dorzolamide-treated eyes.

**DISCUSSION**

**Pachometry**

The deswelling rate, or PRPH, did not differ significantly between the groups. Corneal thicknesses were also similar, and endothelial permeability was increased in the dorzolamide group. This would suggest that the endothelial pump transfers water at a normal or increased rate in the dorzolamide-treated eyes. This result is puzzling, because inhibition of CA decreases endothelial fluid transport and transendothelial potential in rabbits in vitro and causes corneal swelling by an
unknown mechanism, although these conclusions have been challenged. Several explanations are possible. First, the drug may not have been active against CA. This explanation is unlikely, because the drug decreased the aqueous humor flow rate and intraocular pressure (Table 1). However, the mixture of CA isoenzymes in the endothelial cells is somewhat different from that in the ciliary epithelial cells, therefore, the effects of a specific CA inhibitor may be somewhat different in the two tissues. Second, the drug may not have reached the corneal endothelial cells. This explanation also seems unlikely, because sufficient concentrations of dorzolamide and other CA inhibitors are found in the corneal stromas of rabbits after topical administration, even though the drug pathway to the ciliary epithelium appears to be through the sclera. There was also no statistically significant difference between the groups in the swelling induced by 2 hours of hypoxic contact lens wear, which causes corneal epithelial hypoxia and subsequent stromal swelling that can be accounted for by the consequent increase in stromal lactate concentration. Previous stromal acidosis results in less hypoxia-induced swelling. Because we did not find a difference in swelling, acute administration of dorzolamide probably does not induce clinically significant corneal stromal acidosis. However, a difference in swelling of less than 12 μm or 2.1% was not detectable in this study (Table 1).

**Fluorophotometry**

We found that the endothelial permeability during hypoxia (AM) did not differ significantly between the treatment and control groups. This finding was consistent with similar

<table>
<thead>
<tr>
<th>Measurement</th>
<th><strong>Control Eyes</strong></th>
<th></th>
<th><strong>Dorzolamide Eyes</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Deswelling rate constant, D (min⁻¹)</td>
<td>0.016 ± 0.006</td>
<td>0.014 ± 0.005</td>
<td>0.007</td>
<td>&gt;0.10§</td>
</tr>
<tr>
<td>Percent recovery per hour (%/hr)</td>
<td>59.6 ± 14.5</td>
<td>55.7 ± 13.6</td>
<td>17.1</td>
<td>&gt;0.10§</td>
</tr>
<tr>
<td>Open eye steady-state (OESS) thickness (μm)</td>
<td>561 ± 41</td>
<td>565 ± 47</td>
<td>12</td>
<td>0.14</td>
</tr>
<tr>
<td>8:00 AM thickness (μm)</td>
<td>569 ± 39</td>
<td>572 ± 49</td>
<td>15</td>
<td>0.53</td>
</tr>
<tr>
<td>Induced swelling (μm)</td>
<td>59 ± 19</td>
<td>62 ± 17</td>
<td>16</td>
<td>0.43</td>
</tr>
<tr>
<td>Induced swelling (%)</td>
<td>10.2 ± 3.1</td>
<td>10.9 ± 3.1</td>
<td>2.9</td>
<td>0.36</td>
</tr>
<tr>
<td>Endothelial permeability, AM thickness (μm/min)</td>
<td>3.97 ± 1.01</td>
<td>4.27 ± 0.94</td>
<td>1.19</td>
<td>0.28</td>
</tr>
<tr>
<td>Endothelial permeability, PM (×10⁻⁴ cm/min)</td>
<td>4.10 ± 0.80</td>
<td>4.40 ± 0.84</td>
<td>0.43</td>
<td>0.01</td>
</tr>
<tr>
<td>Intraocular pressure change (%)§</td>
<td>−4.8 ± 12.1</td>
<td>−15.4 ± 14.1</td>
<td>7.7</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Aqueous humor flow rate (μl/min)</td>
<td>3.08 ± 0.74</td>
<td>2.83 ± 0.52</td>
<td>0.43</td>
<td>0.02</td>
</tr>
<tr>
<td>Corneal autofluorescence 457.9 nm (ng/ml fluorescein equivalents)</td>
<td>3.76 ± 1.23</td>
<td>3.85 ± 1.15</td>
<td>0.42</td>
<td>0.35</td>
</tr>
<tr>
<td>Corneal autofluorescein 488 nm (ng/ml fluorescein equivalents)</td>
<td>2.39 ± 0.37</td>
<td>2.39 ± 0.39</td>
<td>0.22</td>
<td>0.99</td>
</tr>
<tr>
<td>Endothelial cell density (cells/mm²)</td>
<td>2899 ± 327</td>
<td>2807 ± 317</td>
<td>160</td>
<td>0.02</td>
</tr>
<tr>
<td>Coefficient of variation of cell area</td>
<td>0.26 ± 0.04</td>
<td>0.25 ± 0.04</td>
<td>0.02</td>
<td>0.11</td>
</tr>
<tr>
<td>Hexagonal endothelial cells (%)§</td>
<td>65 ± 10</td>
<td>67 ± 8</td>
<td>8</td>
<td>&gt;0.10§</td>
</tr>
</tbody>
</table>

* SD = standard deviation of the differences between paired eyes.
† Two-tailed, paired Student's t-test.
‡ MDD = minimum detectable difference with 90% power (α = 0.05; β = 0.10).
§ Signed rank test.
II [100 IOP] − [IOP] ] × 100. (IOP = intraocular pressure).
# Measured from baseline endothelial photographs taken before administration of dorzolamide.
**FIGURE 1.** Corneal deswelling rate plotted as percent recovery per hour (PRPH). The horizontal lines show the mean values for the control (59.6%) and dorzolamide (55.7%) groups. Deswelling rates for the two eyes of each subject are marked by identical symbols and connected by straight lines.

**FIGURE 2.** Normoxic endothelial permeability (PM permeability) after the period of hypoxic contact lens wear. The horizontal lines show the mean normoxic permeabilities for the control ($4.10 \times 10^{-4}$ cm/minute) and dorzolamide ($4.40 \times 10^{-4}$ cm/minute) groups. Permeabilities for the two eyes of each subject are marked by identical symbols and connected by straight lines.
TABLE 2. Corneal Endothelial PM Permeabilities for the Placebo Eyes of Six Subjects Involved in the Present Study (Swollen Cornea) and the Previous Study (Unswollen Cornea)  

<table>
<thead>
<tr>
<th>Permeability (× 10^-4 cm/min)</th>
<th>Mean</th>
<th>SD</th>
<th>P value</th>
<th>MDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swollen</td>
<td>4.05</td>
<td>1.05</td>
<td>&gt;0.10</td>
<td>0.64</td>
</tr>
<tr>
<td>Unswollen</td>
<td>4.07</td>
<td>0.51</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Two-tailed, paired Student's t-test.
† MDD = minimum detectable difference with 90% power (a = 0.05; β = 0.10).

amounts of induced swelling in the two groups (Table 1). The permeability during normoxic recovery (PM permeability), however, was significantly higher in the treatment group. This result was confirmed by our calculations from fluorescence data of a previous study in which the corneas were not swollen (Table 3). Prolonged stromal acidosis, if caused by dorzolamide, would not account for this finding. Acidosis causes a decrease in the fluorescence efficiency of fluorescein. If stromal acidosis were present during the early part of the PM measurement period, it would produce an underestimation of the PM permeability, not the increase we found. Elevated permeability is consistent with the increase in hydraulic conductivity of the endothelium induced by acetazolamide in rabbit eyes in vitro. It is also consistent with the increase in corneal thickness found in patients taking dorzolamide for 4 weeks. This small increase in permeability did not result in an increase in OESS thickness acutely and may not be clinically significant.

The previous fluorophotometric study of dorzolamide used the same schedule for administration of the drug, but did not induce corneal swelling. For the placebo eyes of the six subjects who were in both studies, there was no significant difference in the values for the PM endothelial permeability, with a minimum detectable difference of 0.64 × 10^-4 cm/minute (Table 2). We therefore consider the PM permeability, which is measured under normoxic conditions during deswelling after previous hypoxia and corrected for changes in corneal thickness, to be similar to the endothelial permeability in the unswollen state.

The aqueous humor flow rate and intraocular pressure were significantly decreased by dorzolamide. This finding confirms those of Maut et al. and points to inhibition of aqueous humor secretion as the mechanism causing the intraocular pressure-lowering effect of the drug.

Specular Microscopy

We found an unexpected statistically significant difference in baseline endothelial cell density between the dorzolamide-treated eyes and placebo-treated eyes in these normal subjects (Table 1). We have no explanation for this finding. The difference was not related to drug administration, because the specular microscopic examinations were performed before any drug or placebo was administered. Perhaps the finding is a Type I error (finding a statistically significant difference when, in fact, no difference exists), of which there is a 2% chance (Table 1). In any case, the mean difference of 92 cells/mm² has no clinical significance, and endothelial cell density was not correlated with any of the functional measurements in the study except for PM permeability in the placebo eyes.

The results of this investigation apply only to the acute administration of dorzolamide to normal, young subjects after a brief hypoxic stress. One may draw different conclusions when studying subjects who have used dorzolamide for the chronic treatment of glaucoma or groups with decreased PRPH values such as older subjects, contact lens wearers, and patients with Fuchs' corneal dystrophy or penetrating keratoplasty.

References

Dorzolamide Effects on Corneal Endothelial Function


