Additive Effect of Dorzolamide on Aqueous Humor Flow in Patients Receiving Long-term Treatment With Timolol

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Objective: To determine the additive effect on aqueous humor flow of short-term dorzolamide treatment in patients with glaucoma receiving long-term treatment with timolol.

Subjects and Methods: Thirty-nine patients with glaucoma, 19 at Mayo Clinic, Rochester, Minn, and 20 at the University of Uppsala, Uppsala, Sweden, who had been receiving timolol treatment in both eyes for at least 1 year were studied. Aqueous flow was measured with fluorophotometry and intraocular pressure with tonometry. The effect of dorzolamide was compared with placebo when added to the long-term treatment regimen with timolol.

Results: Dorzolamide reduced aqueous humor flow by 24% ± 11% (mean ± SD). The intraocular pressure as compared with placebo in the US cohort was reduced by 10% ± 6% and in the Swedish cohort by 18% ± 9%.

Conclusions: Dorzolamide, a carbonic anhydrase inhibitor, has additive effects as an ocular hypotensive agent with timolol, a β-adrenergic antagonist, even though both drugs are suppressors of aqueous humor flow. Dorzolamide’s effect on flow in these patients is the same as reported previously in normal subjects who are not taking a β-adrenergic antagonist.


Dorzolamide hydrochloride is a carbonic anhydrase inhibitor, a class of drugs known to lower intracocular pressure by the inhibition of aqueous inflow into the anterior chamber. Inhibition of inflow is also the mechanism by which β-adrenergic antagonists, such as timolol, betaxolol, and levobunolol, lower intraocular pressure. From a clinical perspective, it would be helpful to know if persons who are receiving long-term treatment with β-adrenergic antagonists would benefit by the addition of dorzolamide.

Several published studies address this question. Nardin et al1 found that the addition of MK-507 (dorzolamide) to patients receiving treatment with timolol reduced intraocular pressure an additional 13% to 21%. Strahlman et al2 compared the efficacy of dorzolamide with that of timolol and betaxolol and added dorzolamide therapy to a subset of their patients who were therapeutic “failures” while receiving a single therapy. When dorzolamide was added to timolol (23 patients), there was a 13% additional lowering of intraocular pressure at the trough of its effect. The following year, Strahlman et al3 found that dorzolamide lowered intraocular pressure 14% more than placebo in patients receiving a long-term regimen of timolol.

Wayman et al4 have studied the effect on aqueous humor flow of short-term doses of dorzolamide and timolol combined in normal human subjects. They found that dorzolamide caused an additional 17% suppression of aqueous humor flow when added to a short-term regimen of timolol in normal subjects.

This article describes the effect on aqueous humor flow of adding short-term dorzolamide treatment to the regimen of patients with glaucoma already receiving long-term treatment with a β-adrenergic antagonist, timolol.

RESULTS

Table 1 summarizes the flow of aqueous humor under the conditions of the study in the patients from the 2 medical centers. There were no significant differences between the results of flow in the eyes that received placebo first and those that received dorzolamide first, so the results in the 2 eyes of each patient were combined. Also, there were no significant differences.
SUBJECTS AND METHODS

The study was carried out in 2 centers: the University of Uppsala, Uppsala, Sweden, and the Mayo Clinic, Rochester, Minn. Each institution recruited patients who had been using timolol for at least 1 year. The 20 patients at the University of Uppsala consisted of 12 women and 8 men between the ages of 49 and 78 years with a mean age of 67 years, 17 of whom had chronic simple glaucoma, 2 of whom had suspected glaucoma, and 1 of whom had exfoliation syndrome with glaucoma. The 19 patients at the Mayo Clinic consisted of 11 women and 8 men between the ages of 23 and 79 years with a mean age of 58 years, 15 of whom had chronic simple glaucoma and 4 of whom had suspected glaucoma. All potential subjects underwent an eligibility examination that included a medical and ophthalmic history, slitlamp examination, visual acuity testing, applanation tonometry, and ophthalmoscopy. Exclusion criteria included allergy to fluorescein or sulfonamides, narrow palpebral fissures, photophobia, pregnancy, active breast-feeding, use of systemic β-adrenergic antagonists, history of ocular disease or surgery, or evidence of an acute illness.

Patients were studied on 2 days so that each eye could be treated with dorzolamide and placebo and the results compared. The 2 studies were separated by 1 week or longer to assure that the effect of dorzolamide had disappeared. During this period the subjects continued to use timolol ophthalmic drops as prescribed by their physician. On the first day we compared the effects of the addition of 2% dorzolamide hydrochloride (Trusopt, Merck & Co Inc, Whitehouse Station, NJ) on the aqueous flow of one eye with the effects of a placebo (Hypo Tears, IOLAB, Claremont, Calif) on the flow of the other eye. On the second day, dorzolamide and placebo were instilled in the opposite eyes and the measurements of flow were repeated.

The day before aqueous flow measurements were performed, the subjects reported to the testing site. The investigator instilled 1 drop (about 20 µL) of 2% dorzolamide hydrochloride in one eye and 1 drop of placebo in the other eye at 8 AM, noon, and 5 PM. Drops were reinstitled on the day of measurement at 8 AM and noon. After a washout period of at least 1 week, the entire procedure was repeated but dorzolamide and placebo were instilled in the opposite eyes.

Sterile dropper bottles containing either 2% dorzolamide hydrochloride or a placebo were labeled “right eye” or “left eye” to mask both the patients and the investigators. The experimental drops were instilled by the investigators.

Fluorescence of the cornea and anterior chamber was measured every 2 hours between 8 AM and 4 PM to determine the rate of disappearance of fluorescein that had been self-instilled by the subjects at 2 AM. Following the 4 PM measurement of fluorescence, intraocular pressure was measured 3 times with a Goldmann tonometer, alternating between the 2 eyes. The intraocular pressure of each eye was recorded as the average of the 3 measurements.

Fluorescence was measured with a Fluorotron Master (Coherent Radiation, Palo Alto, Calif) in Uppsala and with a 2-dimensional scanning ocular fluorophotometer at Mayo Clinic.

Aqueous humor flow was calculated from the clearance of fluorescein from the anterior chamber after subtracting 0.25 µL/min, the assumed rate of diffusional loss of fluorescein from the system. The equation used was

\[ \text{Flow} = \text{Clearance} = \frac{\Delta C}{C \times \Delta t} \]

where \( \Delta C \) is the fluorescein lost from both the cornea and the anterior chamber during a period of time (\( \Delta t \)), and \( C \) is the average concentration of fluorescein in the anterior chamber during the period of time. The volume of the anterior chamber of patients at Mayo Clinic were determined by photogrammetry; in Uppsala, the volume of every chamber was assumed to have the normal average value of 200 µL. (The volume of the anterior chamber is one determinant of the calculated rate of aqueous humor flow, but because each eye is being compared with itself and because dorzolamide is not known to affect the depth of the anterior chamber, this assumption would not affect the calculation.)

A Student 2-sided t test for paired samples was used to test the flow differences between paired eyes for statistical significance. \( P < .05 \) was considered statistically significant. A sample size of 20 subjects provides a power of 95% for detecting a 13% difference in the flow of one eye as compared with its fellow eye on the same day. For comparison of the flow in the same eye on 2 different occasions, a sample size of 20 subjects has a power of 95% to detect a difference of 17%. Results are reported as mean ± SD.

The experiment did not measure the rate of aqueous humor flow in the untreated eyes of these subjects. However, it has been shown that aqueous humor flow is normal in patients with untreated glaucoma. The rate of

between the results of flow in the 2 centers and the 2 groups were combined into a single group of 39 patients.

The flow rate in the eyes when placebo was given was 1.88 ± 0.53 µL/min. This relatively low rate, compared with the daytime flow of normal humans, 2.97 ± 0.77 µL/min, was due to the long-term use of β-adrenergic antagonists.

When dorzolamide was given, the flow rate decreased to 1.42 ± 0.44 µL/min (\( P < .001 \)). The average decrease in aqueous humor flow in all 39 patients caused by the addition of dorzolamide compared with placebo was 0.46 µL/min. This is 15% of the normal rate of aqueous flow and 24% of the β-adrenergic antagonist–suppressed rate of aqueous flow.

The decrease of aqueous humor flow predictably caused a reduction of intraocular pressure. Table 2 summarizes the effects on intraocular pressure in the 2 medical centers. Each eye of each patient served as its own control. The average reduction of intraocular pressure at Mayo Clinic was 9% ± 6%; at the University of Uppsala, it was 18% ± 9%. The response of intraocular pressure to dorzolamide at the 2 study centers was significantly different (\( P = .01 \)). For this reason, the responses and statistical analyses are shown only separately for the 2 centers rather than combining them.

COMMENT

The experiment did not measure the rate of aqueous humor flow in the untreated eyes of these subjects. However, it has been shown that aqueous humor flow is normal in patients with untreated glaucoma. The rate of
were all receiving long-term treatment with timolol. For the group of patients in this study, the untreated rate of aqueous flow would be expected to be somewhat less because aqueous flow diminishes with age and the average age of the combined group was 63 years.

**Table 3** lists the rates of aqueous flow in this study along with those of 2 previous studies of aqueous humor flow and dorzolamide. The table shows that there is good consistency from study to study on the rate of aqueous humor flow during the day. The table also concludes that the effect of dorzolamide is partly additive to the β-adrenergic antagonist timolol when both drugs are given to previously untreated subjects. If one compares the flow reduction of dorzolamide alone in normal subjects (0.54 µL/min) with the flow reduction in patients receiving long-term treatment with timolol (0.46 µL/min), one can conclude that dorzolamide exerts its full effect in combination with timolol; ie, that the 2 drugs are additive.

This is a study of patients with glaucoma who are receiving long-term timolol in which the effects of the test drug were measured after administration for less than 24 hours. These facts must be kept in mind when comparing this study with others. Also, because suppression of flow will cause a proportional suppression of the outflow pressure of the eye rather than the intraocular pressure, the effect on intraocular pressure will vary according to the untreated intraocular pressure. In general, the higher the untreated intraocular pressure, the greater the percentage lowering of the intraocular pressure for such a drug. If this principle is kept in mind, there is good agreement among this study and the previously cited studies in which dorzolamide was added to a regimen of timolol treatment. The results of this study suggest that a therapeutic trial is rational for patients with glaucoma whose pressure control is borderline while receiving a β-adrenergic antagonist and for whom the target pressure is within reach of 2 to 3 mm Hg additional lowering.

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### REFERENCES


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Table 1. Aqueous Humor Flow 8 AM to 4 PM*

<table>
<thead>
<tr>
<th>Institution (No. of Patients)†</th>
<th>Placebo</th>
<th>Dorzolamide Hydrochloride</th>
<th>% Change (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo Clinic (19)</td>
<td>1.70 ± 0.50</td>
<td>1.23 ± 0.34</td>
<td>−26 ± 14 (&lt;.001)</td>
</tr>
<tr>
<td>University of Uppsala (20)</td>
<td>2.05 ± 0.55</td>
<td>1.60 ± 0.45</td>
<td>−22 ± 8 (&lt;.001)</td>
</tr>
<tr>
<td>Combined groups (39)</td>
<td>1.88 ± 0.55</td>
<td>1.42 ± 0.44</td>
<td>−24 ± 11 (&lt;.001)</td>
</tr>
</tbody>
</table>

*All data are presented as mean ± SD micrometers per liter. The patients were all receiving long-term treatment with timolol. †Mayo Clinic is in Rochester, Minn; University of Uppsala, Uppsala, Sweden.

Table 2. Intraocular Pressure at 4 PM*

<table>
<thead>
<tr>
<th>Institution (No. of Patients)†</th>
<th>Placebo</th>
<th>Dorzolamide Hydrochloride</th>
<th>% Change (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo Clinic (19)</td>
<td>18.1 ± 2.5</td>
<td>16.5 ± 2.1</td>
<td>−9 ± 6 (&lt;.001)</td>
</tr>
<tr>
<td>University of Uppsala (20)</td>
<td>17.4 ± 1.8</td>
<td>14.3 ± 1.9</td>
<td>−18 ± 9 (&lt;.001)</td>
</tr>
</tbody>
</table>

*All data are presented as mean ± SD millimeters of mercury. The patients were all receiving long-term treatment with timolol. †Mayo Clinic is in Rochester, Minn; University of Uppsala, Uppsala, Sweden.

Table 3. Results of Previous Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Conditions</th>
<th>Aqueous Flow, µL/min</th>
<th>Absolute Reduction of Flow, µL/min</th>
<th>Percent Reduction of Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maua et al*</td>
<td>No treatment</td>
<td>3.18</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>Wayman et al*</td>
<td>No treatment</td>
<td>3.07</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>Timolol (short-term)</td>
<td>Adding dorzolamide to short-term timolol</td>
<td>1.37</td>
<td>0.27</td>
<td>16</td>
</tr>
<tr>
<td>Current study (long-term)</td>
<td>Timolol (long-term)</td>
<td>1.87</td>
<td>. . .</td>
<td>. . .</td>
</tr>
<tr>
<td>Adding dorzolamide to long-term timolol</td>
<td>1.41</td>
<td>0.46</td>
<td>24</td>
<td></td>
</tr>
</tbody>
</table>