Aqueous Humor Flow in Human Eyes Treated With Dorzolamide and Different Doses of Acetazolamide

Lill-Inger Larsson, MD, PhD; Albert Alm, MD, PhD

Objective: To measure the effect of topically applied 2% dorzolamide hydrochloride (Trusopt, Merck & Co Inc, Whitehouse Station, NJ) and different doses of orally administered acetazolamide (Diamox, Lederle Ophthalmic Pharmaceuticals, Pearl River, NY), alone and in combination, on aqueous humor flow.

Design: A randomized, double-masked, placebo-controlled study of 20 human subjects was carried out. Aqueous humor flow was measured by clearance of topically applied fluorescein. Serum standard bicarbonate and serum acetazolamide levels were analyzed.

Results: Treatment with dorzolamide reduced aqueous flow by 17%, and a maximum dose of acetazolamide alone reduced flow by 29%. Increasing doses of acetazolamide alone gradually decreased flow, while small doses of acetazolamide did not suppress flow further when dorzolamide was already applied topically. Serum acetazolamide concentrations rose with increasing doses of acetazolamide. Serum standard bicarbonate levels were all in the normal range.

Conclusions: Treatment with dorzolamide reduced aqueous humor flow statistically significantly (2.50 µL/min vs 3.00 µL/min; \(P = .001\)) compared with placebo, but less than a maximum dose of acetazolamide. Small doses of acetazolamide added to dorzolamide treatment did not further enhance the decrease in flow. Since there was no metabolic acidosis as measured by plasma levels of standard bicarbonate, the decrease in aqueous flow could be attributed to the direct action of the carbonic anhydrase inhibitors on the carbonic anhydrase enzymes. It is concluded that the smaller effect of dorzolamide, as compared with acetazolamide, is due to insufficient inhibition of at least 1 of the 2 carbonic anhydrase isozymes involved in aqueous humor production.


From the Department of Ophthalmology, Uppsala University Hospital, Uppsala, Sweden.
There was no obvious explanation for the lower effect of 17%, while acetazolamide suppressed the flow by 30%. The other explanation is that dorzolamide causes a less complete inhibition of the CAs involved compared with hydrochloride was given in one eye, and 1 drop of placebo in the other eye. This procedure was repeated at noon and 5 PM. The subjects were instructed to awaken at 2 AM on day 2 and instill 1 drop of 2% fluorescein into each eye 3 to 5 times, according to age, at 3-minute intervals and then return to sleep. The subjects then reported to the research area at 8 AM and fluorophotometric measurements of the cornea and anterior chamber were performed. Fluorophotometry was repeated every other hour until 4 PM. After the last fluorophotometric reading at 4 PM, the intraocular pressure was measured with a Goldmann tonometer. On day 2, the same eye drops were given after the measurements at 8 AM and at noon. In addition to the eye drops, an oral capsule of acetazolamide or placebo was given at 8 AM and noon. After the tonometry at 4 PM, 2 blood samples were drawn for analysis of acetazolamide and standard bicarbonate levels in serum.

Fluorescence was measured with a fluorophotometer (Fluorotron Master, Coherent Radiation, Palo Alto, Calif). Aqueous humor flow was calculated from the clearance of fluorescein at each 2-hour interval with the following equation:

\[
\text{Clearance} = \frac{\Delta M}{(Ca \times \Delta t)}
\]

where \(\Delta M\) is the loss of mass of fluorescein in the combined cornea and anterior chamber during an interval \((\Delta t)\), and \(Ca\) is the average concentration in the anterior chamber during the interval, estimated from the initial and final fluorescence and assuming a single exponential decay. Aqueous humor flow was determined from the rate of clearance of fluorescein after subtracting the presumed rate of diffusional clearance (0.25 \(\mu\)L/min).21

The blood samples that were drawn on day 2 were handled immediately. Analysis of serum standard bicarbonate levels was performed at the chemical laboratory at Uppsala University Hospital, Uppsala Sweden. The reference range for serum bicarbonate was 23 to 33 mmol/L. The samples for acetazolamide level analysis were centrifuged, and the plasma was collected and frozen at 70°C. At the end of the study all these frozen samples were sent to David Berry, PhD, Medical Toxicology Unit, Guy’s & St Thomas’ Hospital Trust, London, England, for analysis of acetazolamide levels in serum.28,29

The Student 2-sided \(t\) test for paired samples was used for the statistical analysis. A \(P < 0.05\) was considered statistically significant. In previous studies, the normal aqueous humor flow rate in daytime has been measured to be 2.7±0.63 \(\mu\)L/min (mean±SD).20 A sample size of 20 in each group would provide a power of 95% for detecting a true difference of 20% between the 2 eyes.31

Subjects, Materials, and Methods

Twenty normal subjects were included in the study. There were 11 women and 9 men and the mean age was 31.7 years (range, 20-49 years). Medical and ophthalmological histories were taken for all subjects. They also underwent an ophthalmic screening examination consisting of visual acuity testing, slitlamp examination, applanation tonometry, and ophthalmoscopy. Exclusion criteria were ocular disease, systemic disease requiring long-term medical treatment, inability to comply with tonometry or fluorophotometry, an intraocular pressure difference between the 2 eyes greater than 3 mm Hg, history of kidney stones, and known drug hypersensitivity (especially to sulfonamide derivatives). The research protocol was approved by the Ethical Committee of Uppsala University, Uppsala, Sweden, and informed consent was obtained from all participants.

The study was performed in 4 parts and the sequence of the 4 parts was randomized. In part 1, the effect of 2% dorzolamide vs placebo was studied when the subjects received oral administration of placebo capsules. Parts 2 through 4 were identical to part 1 except that the oral placebo capsules were replaced by acetazolamide capsules; 31.3 mg in part 2, 62.5 mg in part 3, and 250 mg in part 4. There was a washout period of at least 14 days between all parts of the study to ensure complete elimination of the drugs.

The study was randomized, double-masked, and placebo-controlled. The dorzolamide and placebo eye drops, as well as the acetazolamide and placebo capsules, were given by random assignment and were administered from identically appearing containers labeled by subject number, sequence, and, where appropriate, eye. The active ingredient in the eye drops was 2% dorzolamide (Trusopt, Merck & Co Inc, Whitehouse Station, NJ), and artificial tears were used as placebo eye drops (Isopo-Plain, Alcon Laboratories, Ft Worth, Tex). Acetazolamide tablets (Diamox, Leede Ophthalmic Pharmaceuticals, Pearl River, NY), ground to a fine powder, were used as the active drug in the oral capsules, and identically appearing placebo capsules were prepared without the active ingredient. Half the subjects received dorzolamide in the right eye, and half received it in the left eye. Also, the oral capsules were equally randomized between the different parts of the study.

Each part of the study was performed on 2 consecutive days (Figure 1). On day 1 the subjects reported to the test area at 8 AM. One drop (~20 \(\mu\)L) of 2% dorzolamide hydrochloride was given in one eye, and 1 drop of placebo in the other eye. This procedure was repeated at noon and 5 PM. The subjects were instructed to awaken at 2 AM on day 2 and instill 1 drop of 2% fluorescein into each eye 3 to 5 times, according to age, at 3-minute intervals and then return to sleep. The subjects then reported to the research area at 8 AM and fluorophotometric measurements of the cornea and anterior chamber were performed. Fluorophotometry was repeated every other hour until 4 PM. After the last fluorophotometric reading at 4 PM, the intraocular pressure was measured with a Goldmann tonometer. On day 2, the same eye drops were given after the measurements at 8 AM and at noon. In addition to the eye drops, an oral capsule of acetazolamide or placebo was given at 8 AM and noon. After the tonometry at 4 PM, 2 blood samples were drawn for analysis of acetazolamide and standard bicarbonate levels in serum.

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Hydroflow in monkeys. Yamazaki et al18 found increased flare, measured by laser-flare cell photometry, in 6 human subjects given single doses of dorzolamide, and they interpreted the results as evidence for reduced aqueous humor flow. Another topical CA inhibitor, 6-amino-2-benzothiazole-sulfonamide, reduced aqueous humor production in human eyes.22 A recent study by Maus and coworkers23 compared the efficacy of topically administered dorzolamide as a suppressor of aqueous humor flow in humans to that of a maximal oral dose of acetazolamide. Dorzolamide suppressed aqueous humor flow by 17%, while acetazolamide suppressed the flow by 30%. There was no obvious explanation for the lower effect of dorzolamide, which in vitro is an effective inhibitor of CA isozyme II.24 One possible explanation is that part of the flow reduction obtained with a full dose of acetazolamide is unrelated to local CA inhibition. Acetazolamide causes a metabolic acidosis with time, and it has been suggested that a local acidic environment contributes to the flow reduction.25 In the previous study by Maus et al,23 levels of serum bicarbonate were not determined, but the treatment period was short and a marked metabolic acidosis is an unlikely explanation for the difference in potency between the 2 studied drugs. Another explanation is that dorzolamide causes a less complete inhibition of the CAs involved compared with...
acetazolamide. Recent studies have shown that CA isozyme IV is also involved in the production of aqueous humor.26 We decided to test these 2 possibilities by determining the effect of dorzolamide and various doses of acetazolamide, alone and in combination, on aqueous humor flow and serum bicarbonate levels.

RESULTS

One subject had marked myopia (−3.5 diopters) in both eyes in the evening of day 2 of her second part of the study. The myopia slowly resolved and the refraction returned to normal within 48 hours. The randomization code was broken for this subject, and it was revealed that she had received the highest dose of acetazolamide (250 mg given twice) on this particular day. She was thereafter withdrawn from the study, but data from the 2 already completed parts were included in the analysis. During the course of the study 1 female subject was diagnosed with a malignant breast tumor and therefore was excluded. The remaining 18 subjects completed the study.

The results on the aqueous humor flow in eyes treated with placebo eye drops and corresponding results for dorzolamide-treated eyes are presented in Table 1. The lowest dose of acetazolamide had no statistically significant effect but higher doses of acetazolamide gradually suppressed aqueous humor flow in eyes receiving topical placebo. The maximum dose of 250 mg of acetazolamide given twice (corresponding to a total daily dose of 1000 mg of acetazolamide) reduced flow by 29% compared with placebo eye drops (P<.001). Dorzolamide alone suppressed flow by 17% compared with placebo (2.50 µL/min vs 3.00 µL/min; P=.001), which was almost twice the flow suppression obtained with an oral dose of acetazolamide of 62.5 mg given twice (corresponding to a daily dose of 250 mg of acetazolamide), but less than that of an acetazolamide dose of 250 mg given twice (Table 1). In the dorzolamide-treated eyes, the lower doses of acetazolamide did not add any further suppression of flow; it was only the highest dose of acetazolamide (250 mg given twice) that reduced the aqueous humor flow in a statistically significant way (16% compared with oral placebo capsules [P<.001]).

When equal doses of acetazolamide were given, there was a statistically significant difference in flow between eyes receiving placebo and eyes receiving dorzolamide at the lower doses of acetazolamide, but not when the maximum dose was administered (Figure 2). When untreated eyes (placebo drops and placebo capsules) were compared with maximally treated eyes (dorzolamide drops and 250-mg acetazolamide capsules), there was a difference in flow of 30% (P<.001). The time courses of flow under the different experimental conditions are shown in Figure 3 and show the effect of time of day. There was no great difference in reduction of aqueous humor flow between the 2-hour intervals 10 AM to noon and 2 to 4 PM.

The intraocular pressures at 4 PM for eyes receiving placebo and for dorzolamide-treated eyes are summarized in Table 2. The results are in concordance with the results from the flow measurements, but the percent reduction of the intraocular pressure was smaller than the percent reduction of aqueous flow. This difference is expected since the outflow pressure (intraocular pressure minus episcleral venous pressure) rather than the intraocular pressure is reduced in proportion to aqueous humor flow reduction. Also, the subjects all had low initial intraocular pressures.

Serum concentrations of acetazolamide at 4 PM on day 2 of each part of the study are given in Table 3, as well as the serum standard bicarbonate levels. The concentration of acetazolamide in serum was increased with

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**Figure 1. Sequence of events in experimental protocol.**

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**Table 1. Aqueous Humor Flow (8 AM-4 PM) in Eyes Receiving Topical Placebo and Eyes Treated With Topical 2% Dorzolamide**

<table>
<thead>
<tr>
<th>Acetazolamide, mg</th>
<th>No. of Subjects</th>
<th>Aqueous Humor Flow, µL/min</th>
<th>Percent Change (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>vs Acetazolamide, 0 mg</td>
</tr>
<tr>
<td>0</td>
<td>18</td>
<td>3.00±0.62</td>
<td>...</td>
</tr>
<tr>
<td>31.3</td>
<td>18</td>
<td>2.85±0.61</td>
<td>−5 (.16)</td>
</tr>
<tr>
<td>62.5</td>
<td>19</td>
<td>2.73±0.51</td>
<td>−9 (.02)</td>
</tr>
<tr>
<td>250</td>
<td>19</td>
<td>2.14±0.37</td>
<td>−29 (&lt;.001)</td>
</tr>
</tbody>
</table>

**Table 2.** Aqueous Humor Flow (8 AM-4 PM) in Eyes Receiving Topical Placebo and Eyes Treated With Topical 2% Dorzolamide

<table>
<thead>
<tr>
<th>Acetazolamide, mg</th>
<th>No. of Subjects</th>
<th>Aqueous Humor Flow, µL/min</th>
<th>Percent Change (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>vs Acetazolamide, 0 mg</td>
</tr>
<tr>
<td>0</td>
<td>18</td>
<td>2.50±0.50</td>
<td>...</td>
</tr>
<tr>
<td>31.3</td>
<td>18</td>
<td>2.50±0.55</td>
<td>±0 (.22)</td>
</tr>
<tr>
<td>62.5</td>
<td>19</td>
<td>2.41±0.44</td>
<td>−4 (.23)</td>
</tr>
<tr>
<td>250</td>
<td>19</td>
<td>2.11±0.40</td>
<td>−16 (&lt;.001)</td>
</tr>
</tbody>
</table>

*Acetazolamide doses were given twice during the study day (8 AM and noon). Ellipses indicate not applicable. Aqueous flow values are expressed as means±SD.
higher doses of oral acetazolamide. Serum standard bicarbonate levels were all in the normal range. The suppression of aqueous humor flow increased with rising serum levels of acetazolamide (Figure 4).

**COMMENT**

The data from the present study confirm previous results that 2% dorzolamide hydrochloride suppresses aqueous humor formation, but not to the same extent as a maximum dose of acetazolamide. Treatment with dorzolamide alone reduced aqueous flow by 17% in this study, and a maximum dose of acetazolamide alone reduced flow by 29%. Corresponding figures for comparable doses were 17% and 30% in the previously mentioned study. Increasing doses of acetazolamide gradually decreased the aqueous flow. However, small doses of orally administered acetazolamide did not suppress flow further when dorzolamide was already applied topically. Only the highest dose of acetazolamide (250 mg) resulted in accentuated suppression of the aqueous humor flow.

In the present study we administered 3 doses of acetazolamide, apart from placebo. The highest dose, 250 mg of acetazolamide given twice (corresponding to a daily dose of 1000 mg of acetazolamide), was chosen to ensure a maximal effect, and also to use the same oral dose as was used in the study by Maus et al to be able to make adequate comparisons of effects on flow. The aim of the study was to see if a low dose of acetazolamide, with few systemic adverse effects, could enhance the aqueous flow suppression obtained with dorzolamide. For that purpose we decided to test 2 low doses of acetazolamide, 31.3 mg and 62.5 mg, and follow the effect on aqueous flow after a first and second administration of these doses. Acetazolamide was administered in gelatin capsules that we expected to be rapidly dissolved in the stomach and not to retard uptake of acetazolamide into plasma. Peak plasma levels after oral acetazolamide are reached about 2 hours after the dose and start to decline rapidly after 6 hours. Thus, aqueous flow between 10 AM and noon corresponds to the peak effect of the single dose. The effects observed between noon and 2 PM correspond to a dose that is somewhat higher than the single dose, because another dose of acetazolamide was given at noon. Neither dose caused a marked improvement of the effect on aqueous flow after noon, which indicates that all 3 doses were at flat parts of the dose-response curve, the 2 lower doses at the low end and the highest dose at the top.

The reduction of aqueous humor flow by dorzolamide treatment alone was almost twice that obtained with an oral dose of 62.5 mg of acetazolamide given twice, but definitely lower than the reduction in flow obtained by 250 mg of acetazolamide given twice. The addition of 31.3 or 62.5 mg of acetazolamide to dorzolamide did not suppress the aqueous humor production any further (P = .22 and P = .23). If the mechanism of action is identical for the 2 drugs, some additivity would be expected, at least with 62.5 mg, which caused a statistically significant effect in eyes that received the topical placebo. The maximal intraocular pressure–lowering effect has earlier been shown to occur at plasma concentrations of acetazolamide between 5 and 10 µg/mL. The mean plasma concentration achieved with 62.5 mg of acetazolamide given twice, 4.3 µg/mL (Table 3), was just below this level.

One explanation for the lack of additivity could be that dorzolamide and acetazolamide act differently on the different CA isozymes. There are at least 7 different CA isozymes, and 2 of them have been found in the ciliary...
epithelium; the cytoplasmic CA II and the membrane-bound CA IV. Both CA II and CA IV seem to coexist in epithelial cells that perform acid-base work, i.e., in cells secreting hydrogen ions either at the luminal or basolateral membranes. It has been suggested that CA IV is the critical enzyme for secretion, because many secretory cells have vectorial properties, with the secretion of ions directed toward basal or apical surfaces. In a recent study by Matsui and coworkers, both CA isozymes in the ciliary epithelium were suggested to be involved in aqueous humor production: the cytoplasmic (CA II) and the membranal (CA IV). The action of the nonpigmented epithelium basolateral membranal CA IV was suggested to be linked to the chloride-bicarbonate exchanger. The inhibitory concentration of dorzolamide for human CA II was 0.2 nmol/L. Maren has reported that the equilibrium dissociation constants at room temperature for dorzolamide with CA II and CA IV are 8 and 300 nmol/L, respectively, and that with an expected tissue concentration of 10 µmol/L after application of a 2% dorzolamide solution, the fractional inhibitions of CA II and CA IV are 0.999 and 0.970, respectively.

If the effect of the 2 CA inhibitors is explained solely by enzyme inhibition, our results indicate that a part of the active enzyme is not affected by dorzolamide and that this portion of CA is affected only when acetazolamide is administered in a dose large enough to be effective on its own. It seems reasonable to assume that dorzolamide effectively inhibits only 1 of the isozymes involved in aqueous humor production. Whether that is due to the higher equilibrium dissociation constant for one of them (CA IV) or to the inability or difficulty of topically applied CA inhibitors to reach and maintain an effective inhibitory concentration at the membrane or in the cytosol cannot be determined from the present study.

Another possibility is that acetazolamide has an effect on aqueous flow that is not related to inhibition of CA in the ciliary processes. Systemic administration of these agents can cause systemic electrolyte disturbances, primarily systemic acidosis, which has been suggested to contribute to the ocular effects. However, we did not find any metabolic acidosis as measured by plasma levels of standard bicarbonate, which makes this explanation less likely.

Addition of twice-daily 2% dorzolamide to the regimen of patients with glaucoma already receiving treatment with timolol or betaxolol has produced a clinically beneficial increase in ocular hypotensive effects. In the present study, we found that treatment with dorzolamide reduced aqueous humor flow and thereby intraocular pressure, but to a lower extent than a max-

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**Table 2. Intraocular Pressure (IOP) at 4 PM in Eyes Receiving Topical Placebo and Eyes Treated With Topical 2% Dorzolamide**

<table>
<thead>
<tr>
<th>Acetazolamide, mg</th>
<th>No. of Subjects</th>
<th>IOP, mm Hg</th>
<th>Percent Change (P) vs Acetazolamide, 0 mg</th>
<th>vs Acetazolamide, 31.3 mg</th>
<th>vs Acetazolamide, 62.5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>18</td>
<td>13.1±1.8</td>
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<td>...</td>
</tr>
<tr>
<td>31.3</td>
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<td>−7 (.05)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>62.5</td>
<td>19</td>
<td>12.0±2.2</td>
<td>−8 (.006)</td>
<td>−1 (.96)</td>
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</tr>
<tr>
<td>250</td>
<td>19</td>
<td>10.4±1.5</td>
<td>−21 (&lt;.001)</td>
<td>−14 (&lt;.001)</td>
<td>−13 (&lt;.001)</td>
</tr>
</tbody>
</table>

**Topical Placebo**

<table>
<thead>
<tr>
<th>Acetazolamide, mg</th>
<th>No. of Subjects</th>
<th>IOP, mm Hg</th>
<th>Percent Change (P) vs Acetazolamide, 0 mg</th>
<th>vs Acetazolamide, 31.3 mg</th>
<th>vs Acetazolamide, 62.5 mg</th>
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<tbody>
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<td>11.5±1.9</td>
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<td>...</td>
</tr>
<tr>
<td>31.3</td>
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<td>11.0±2.5</td>
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<td>−7 (.08)</td>
<td>−2 (.59)</td>
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<tr>
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<td>19</td>
<td>10.1±1.4</td>
<td>−13 (.005)</td>
<td>−8 (.04)</td>
<td>−7 (.11)</td>
</tr>
</tbody>
</table>

*Acetazolamide doses were administered twice during the study day (8 AM and noon). Ellipses indicate not applicable. Intraocular pressure is expressed as mean±SD.

**Table 3. Levels of Serum Acetazolamide and Serum Standard Bicarbonate With Different Doses of Acetazolamide**

<table>
<thead>
<tr>
<th>Acetazolamide, mg</th>
<th>No. of Subjects</th>
<th>Serum Acetazolamide, µg/mL</th>
<th>Serum Bicarbonate, mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>18</td>
<td>0±0</td>
<td>28.7±2.7</td>
</tr>
<tr>
<td>31.3</td>
<td>18</td>
<td>1.8±0.7</td>
<td>28.3±3.0</td>
</tr>
<tr>
<td>62.5</td>
<td>19</td>
<td>4.3±1.7</td>
<td>27.6±4.6</td>
</tr>
<tr>
<td>250</td>
<td>19</td>
<td>16.6±5.9</td>
<td>27.5±2.1</td>
</tr>
</tbody>
</table>

*Acetazolamide doses were administered twice during the study day (8 AM and noon).

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**Figure 4. Aqueous humor flow in eyes receiving topical placebo and their corresponding serum levels of acetazolamide at 4 PM, when oral capsules are given.**

**Table 4. Levels of Serum Acetazolamide and Serum Standard Bicarbonate With Different Doses of Acetazolamide**

<table>
<thead>
<tr>
<th>Acetazolamide, µg/mL</th>
<th>No. of Subjects</th>
<th>Serum Acetazolamide, µg/mL</th>
<th>Serum Bicarbonate, mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>18</td>
<td>0±0</td>
<td>28.7±2.7</td>
</tr>
<tr>
<td>31.3</td>
<td>18</td>
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<td>62.5</td>
<td>19</td>
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<tr>
<td>250</td>
<td>19</td>
<td>16.6±5.9</td>
<td>27.5±2.1</td>
</tr>
</tbody>
</table>
mum dose of orally administered acetazolamide. Small doses of acetazolamide added to dorzolamide treatment did not further enhance the decrease in flow and intraocular pressure. Dorzolamide has the advantage over high doses of acetazolamide that it is well accepted by patients, because intolerable systemic effects are much less likely to occur. However, further studies need to be pursued to know what kind of effects different combinations of dorzolamide and other aqueous suppressors might have on intraocular pressure and aqueous humor flow.

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Reprints: Lill-Inger Larsson, MD, PhD, Department of Ophthalmology, Uppsala University Hospital, S-751 85, Uppsala, Sweden.

REFERENCES


17. W criticized the use of dorzolamide as a first-line therapy, but concluded that its use in combination with other treatment modalities may be beneficial.


