Effect of Dorzolamide Hydrochloride on Central Corneal Thickness in Humans With Cornea Guttata

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Objective: To investigate the effect of dorzolamide hydrochloride on central corneal thickness in humans with cornea guttata.

Design: Randomized, placebo-controlled, double-masked, 2-drug crossover study with 10 patients with cornea guttata and 10 healthy controls, who had mean endothelial cell counts of 988 and 2377 cells/mm^2, respectively. Study medications were 2% dorzolamide and placebo drops applied 3 times a day for 4 weeks. Central corneal thickness measurements using ACMaster (Carl Zeiss Meditec AG, Jena, Germany) and Goldmann applanation tonometry were performed at baseline, 1 day, 1 week, and 4 weeks.

Results: The mean increases in central corneal thickness after 4 weeks in eyes with cornea guttata treated with dorzolamide and placebo were 26.3 µm (95% confidence interval, 8.8 to 43.7) and 3.3 µm (95% confidence interval, –0.5 to 7.1), respectively. No statistically significant changes were measured in the healthy control group. Dorzolamide caused a significant decrease in intraocular pressure ($P < .01$) while placebo did not cause significant changes ($P = .50$).

Conclusion: Application of dorzolamide for 4 weeks resulted in a statistically significant increase in central corneal thickness in patients with compromised corneal endothelium. These results indicate that patients with corneal endothelial problems receiving dorzolamide therapy should be monitored.

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DORZOLAMIDE HYDROCHLORIDE is a potent topical carbonic anhydrase (CA) inhibitor and has been shown to effectively reduce intraocular pressure.[1-4] It is a potent inhibitor of the cytosolic CA isoenzymes II (CA II) and IV (CA IV), both of which are found in the nonpigmented epithelium of the ciliary processes.[5,6] There it inhibits the catalyzed hydration and dehydration of bicarbonate, which is an important step in the ion transport of secretory tissues. The corneal endothelium also possesses the cytosolic CA II as well as the membrane-bound CA IV.[7,8] The isoenzyme CA II plays a major role in keeping the cornea in a relatively steady state of dehydration. The activity of dorzolamide against CA II is 38-fold higher than the activity against CA IV.[9] Thus, dorzolamide is a major inhibitor of CA II and has the potential to interfere with the pump function of the corneal endothelium, which could lead to corneal edema and a concomitant loss in transparency.

These concerns were evaluated in several studies, revealing that dorzolamide was well tolerated and that there were no clinically significant changes in ocular or systemic safety parameters.[10-15] In 1999, Konowal et al[16] performed a retrospective study with 9 eyes of 9 patients who developed irreversible corneal decompensation during dorzolamide therapy. In 2003, Inoue et al[17] detected a statistically significant increase in central corneal thickness (CCT) after long-term use of dorzolamide. However, the CCT measuring methods in these studies did not provide the highest precision because they used optical slitlamp pachymetry or conventional ultrasound pachymetry.

Previously, we showed that short-term application of dorzolamide caused a small but statistically significant increase of CCT in patients with low endothelial cell counts and typical appearance of corneal guttae on slitlamp examination.[18] This finding led us to question whether CCT increases further with a prolonged application of dorzolamide. To answer this question, the present study investigated the long-term effect of dorzolamide on CCT in humans with a low endothelial cell count.

Written informed consent was obtained from all subjects after the nature, scope, and possible consequences of the study had been explained. Our study followed the guidelines of the Declaration of Helsinki and was carried out according to European Union Good Clinical Practice guidelines. The ethics committee of the Medical University of Vienna, Vienna, Austria, approved the study.

SUBJECTS

Twenty subjects (20 eyes) were included in this study: 10 patients with cornea guttata (10 eyes), with the typical appearance of the corneal endothelium on slitlamp examination, and 10 healthy age-matched volunteers (10 eyes). The cornea guttata group consisted of 5 women and 5 men with a mean±SD age of 72±8 years (range, 63-83 years) and a mean±SD endothelial cell count (ECC) of 988±355 cells/mm^2 (range, 475-1495 cells/mm^2). The healthy control group consisted of 7 women and 3 men with a mean±SD age of 70±8 years (range, 60-81 years) and a mean±SD ECC of 2377±249 cells/mm^2 (range, 2013-2825 cells/mm^2). None of the enclosed subjects showed signs of corneal decompensation at the prestudy slitlamp examination.

Inclusion criteria for the cornea guttata group were 60 years or older with an ECC of 1500 cells/mm^2 or fewer and cornea guttata confirmed with endothelial specular microscopy. The control subjects were matched for age, had an ECC of 2000 cells/mm^2 or more, and had a morphologically healthy corneal endothelium as well as no previous surgery. The visual acuity of all study subjects was 20/200 or better, and subjects had an unremarkable medical history and physical examination findings.

Exclusion criteria were relevant ophthalmic diseases, history of hypersensitivity to the trial drug or to drugs with a similar chemical structure, and symptoms of a clinically relevant illness in the 3 weeks before the first study day. We did not include subjects who had had cataract surgery within 3 months or penetrating keratoplasty within 6 months before the first study day as well as subjects who were receiving a systemic or topical CA inhibitor as standard medication.

On the study screening day, all patients underwent a complete ophthalmic examination, including refraction, visual acuity testing, slitlamp biomicroscopy, applanation tonometry, and fundus examination, and were asked in detail about their ophthalmic history. Furthermore, endothelial specular microscopy was performed using a Konan Non-Con Robo SP 8000 (Konan Medical Inc, Tokyo, Japan) to determine corneal ECC.

STUDY DRUGS

The study drugs used in this investigation included dorzolamide (Trusopt 2% eye drops; Merck & Co Inc, Whitehouse Station, New Jersey) and a placebo medication (0.075 mg of benzalkonium chloride in 0.9% saline solution with a pH, density, and osmolarity similar to that of Trusopt). The study medications were put into identical drop bottles and randomized by the pharmacy of the Vienna General Hospital (Vienna, Austria). The randomization list was kept by the pharmacy in a sealed envelope until the end-of-study measurements and completion of data entry.

CCT MEASUREMENT

Central corneal thickness measurements were performed using the ACMaster (Carl Zeiss Meditec AG, Jena, Germany), which was developed for high-precision measurements of CCT, anterior chamber depth, and lens thickness.[19] This measuring tool is based on the principle of dual-beam partial coherence interferometry as was the laboratory prototype version used in our previous study.[18] In all patients and controls, 20 to 30 longitudinal scans were performed at each time point. All scans were saved on compact disc and analyzed using the Zeiss ACMaster software. In our evaluation, we averaged the 10 best A-scans of each time point and used the mean values for data analysis.

STUDY PROTOCOL

This study was conducted in a randomized, placebo-controlled, double-masked, 2-drug crossover design. After we obtained written informed consent, each of the 20 study subjects was given a consecutive study number, which determined the randomized sequence of the study medications for this participant. On the first study day, a baseline CCT measurement was performed using the ACMaster followed by measurement of intraocular pressure (IOP) by Goldmann applanation tonometry.[20] After we demonstrated the drug application, patients were asked to apply 1 drop of study medication 1 every 8 hours (ie, 3 times daily) in the study eye for 28 consecutive days. Central corneal thickness and IOP were measured again 1, 7, and 28 days after baseline measurements; after day 28, each participant discontinued use of study medication 1 and began a 2-week washout period. Afterwards, the second trial phase was initiated following the same protocol but using study medication 2. Central corneal thickness measurements were always done before applanation tonometry. All subjects in this study showed up for all planned visits, and all examinations were carried out between 2 PM and 4 PM.

STATISTICAL METHODS

Corneal scans were analyzed after completion of all study measurements. After the data had been cross-checked and entered into the database, the pharmacy handed over the envelope with the randomization list, the seal was broken, and the medication sequences of the patients were unmasked. A prestudy calculation resulted in a recommended sample size of 10 for the cornea guttata group. Variables of interest are described as mean±SD and range. Mean percentage changes are derived from the geometric mean of the corresponding ratios. Differences between groups are reported indicating means and 95% confidence intervals. The long-term CCT changes in the cornea guttata and control groups were assessed by a linear mixed model. Characteristic features of the crossover trial structure could be efficiently specified within this framework. Central corneal thickness measurements at day 28 and day 0 were considered as outcome and covariate, respectively. Pairwise comparisons between medication within and across groups were adjusted for multiple testing by applying the Tukey-Kramer method. Because considerable heteroscedasticity was observed between groups and medications, a flexible variance/covariance structure was specified to improve the finally reported confidence intervals and pairwise comparison results. The software packages nQuery Advisor (Janet D. Elashoff, Los Angeles, California), SAS (version 9.1; SAS Institute Inc, Cary, North Carolina), and SPSS (version 11.0.1; SPSS Inc, Chicago, Illinois) were used for sample size calculation and statistical analyses. All reported *P* values are the result of 2-sided tests. A significance level of .05 was assumed.

The mean CCT change from baseline to day 28 in the cornea guttata group receiving dorzolamide medication was 26.3 µm (95% confidence interval [CI], 8.8 to 43.7). No
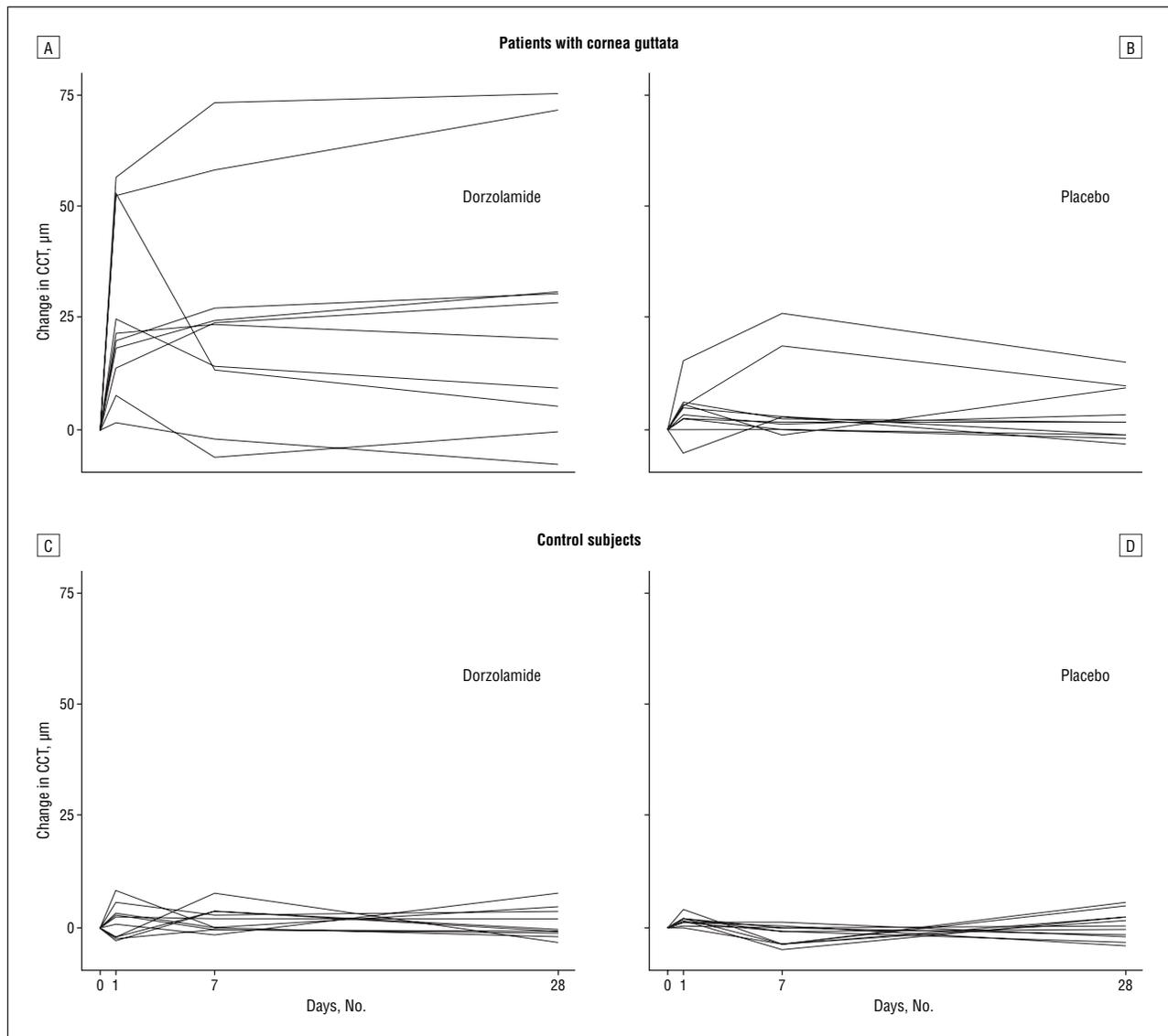
Figure 1. Absolute changes in central corneal thickness (CCT) in 10 patients with cornea guttata treated with dorzolamide hydrochloride (A) and placebo (B) and in 10 control subjects treated with dorzolamide (C) and placebo (D) within 28 days.

further statistically significant change in CCT—neither in the cornea guttata group with placebo medication, nor in the control group using dorzolamide or placebo—was detected when comparing baseline with day 28.

Comparing the groups, we found 2 statistically significant differences from baseline to day 28. The comparisons between the cornea guttata vs the control group both using dorzolamide medication and the cornea guttata group using dorzolamide vs the cornea guttata group using placebo medication showed a mean CCT change of 23.4 µm (95% CI, 9.9 to 37.0) and 23.4 µm (95% CI, 4.3 to 42.5), respectively. The group comparisons between the cornea guttata vs the control group both using placebo medication and the control group using dorzolamide vs the control group using placebo showed a nonsignificant mean CCT change of 2.2 µm (95% CI, −11.3 to 15.7) and 2.1 µm (95% CI, −2.8 to 7.1), respectively.

Figure 1 depicts the changes in CCT of all patients (n=10) in the cornea guttata group with dorzolamide (Figure 1A) and placebo medication (Figure 1B) over the

studied time course. It clearly shows the magnitude and variance of CCT changes, ranging from a −1.5% decrease up to an increase of 14.4% using dorzolamide compared with the minor changes during the placebo treatment. The majority of patients with cornea guttata treated with dorzolamide showed a steep increase in CCT from baseline to study day 1, which was retained with minor changes throughout the rest of the trial phase. The CCT courses of 2 patients attracted attention by showing a high increase of more than 70 µm. In Figure 1B, 2 curves stand out, showing a CCT increase of about 20 and 25 µm after 7 days of placebo treatment and then decreasing for the remaining study phase. Figure 1C and D shows the changes in CCT of the 10 subjects in the control group with dorzolamide (Figure 1C) and placebo medication (Figure 1D) during the study. Only minor changes in CCT are depicted in both graphs.

Table 1 lists the mean±SD CCT and CCT ranges (minimum to maximum) of all patients (n=10) and controls (n=10) using the studied medications at baseline and days 1, 7, and 28.

Table 1. Central Corneal Thickness Over Time of Study Subjects Receiving Study Medication

Study Group	CCT Measurement, Mean ± SD (Range), µm			
	Baseline	Day 1	Day 7	Day 28
Dorzolamide hydrochloride				
Cornea guttata group (n = 10)	557 ± 45 (508-659)	584 ± 44 (515-672)	582 ± 51 (501-682)	583 ± 54 (507-687)
Control group (n = 10)	515 ± 36 (463-579)	516 ± 37 (460-584)	517 ± 37 (464-587)	517 ± 38 (463-591)
Placebo				
Cornea guttata group (n = 10)	558 ± 48 (503-661)	562 ± 47 (505-666)	563 ± 51 (503-679)	561 ± 50 (502-671)
Control group (n = 10)	516 ± 38 (460-586)	518 ± 39 (461-588)	516 ± 38 (462-587)	516 ± 37 (460-584)

Abbreviation: CCT, central corneal thickness.
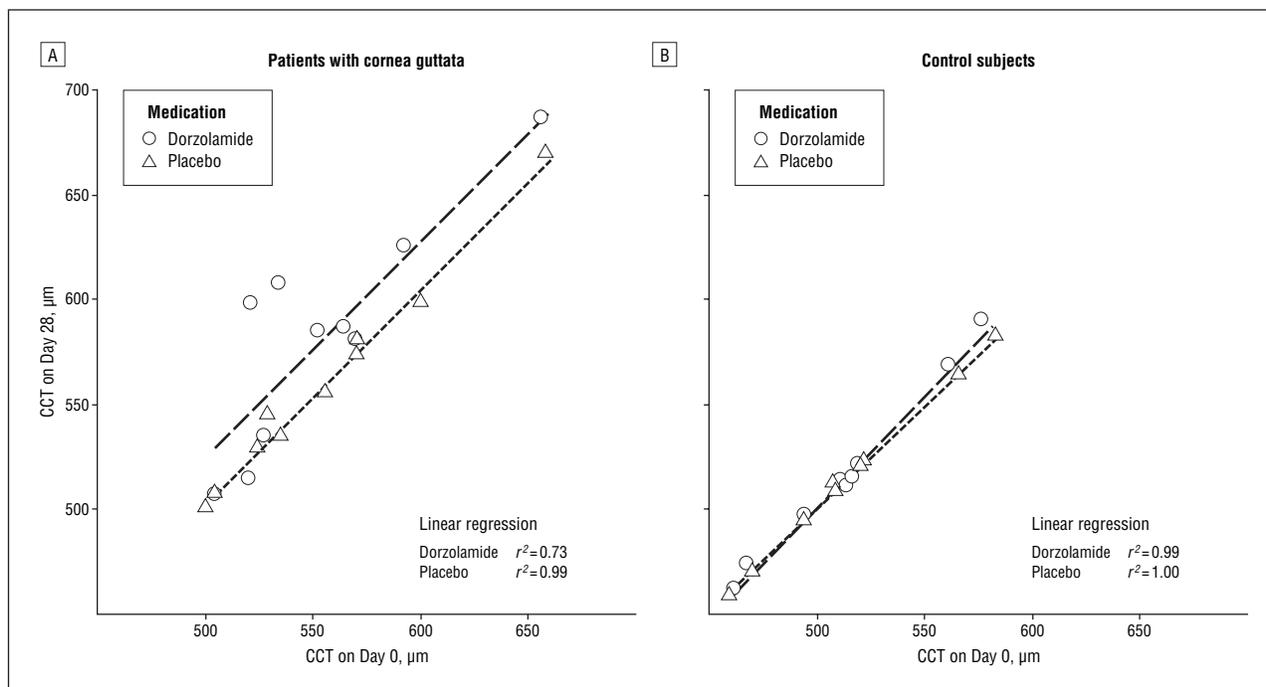
Figure 2. Scatterplots of central corneal thickness (CCT) measurements on day 28 vs day 0 broken down by group (10 patients with cornea guttata and 10 control subjects) and medication. The vertical shift between linear regression lines (dashed indicates dorzolamide hydrochloride; dotted, placebo) shows differences in CCT between medication and placebo.

Figure 2 shows 2 scatterplots with the absolute values of CCT from baseline vs study day 28 using dorzolamide and placebo medication. Figure 2A depicts the CCT values of the patients with cornea guttata; Figure 2B, those of the control subjects. The vertical shift between the linear regression lines depicts the changes in CCT after 28 days of study medication treatment. It can be seen that the absolute CCT values in the cornea guttata group are slightly higher than in the controls. Moreover, the CCT values in the cornea guttata group using dorzolamide are more scattered than in the control group or with placebo medication.

Before starting dorzolamide (n = 20) or placebo (n = 20) treatment, mean ± SD IOPs measured in all study subjects were 12.8 ± 2.7 mm Hg (range, 8-17 mm Hg) and 11.6 ± 3.1 mm Hg (range, 5-17 mm Hg), respectively. Dorzolamide treatment induced a statistically significant decrease in IOP comparing baseline values with values at study days 1, 7, and 28 ($P < .001$). The placebo treatment did not cause statistically significant changes in IOP ($P \geq .30$). **Table 2** outlines changes in IOP (in percentage) during dorzolamide or placebo treatment.

None of the included subjects showed signs of corneal decompensation at the slitlamp examination—either at baseline or at day 1, 7, or 28. However, the baseline CCT was higher for the cornea guttata group as compared with the control subjects. When asked, none of the patients noted any subjective changes in visual acuity during the application of the study medications. One eye in the cornea guttata group had a corneal thickness of 659 µm and should therefore be presumed to have Fuchs endothelial dystrophy. However, the eye did not show signs of corneal decompensation at the slitlamp and also had good visual function. Statistical analysis did not detect any period or carry-over effects in between groups or medications. Central corneal thickness was measured with the ACMaster with an average ± SD precision of 1.4 ± 1.0 µm (range, 0.2-6.0 µm). The average ± SD pre-

Table 2. Changes in Intraocular Pressure Over Time of All Study Subjects Receiving Study Medication

Treatment	IOP Changes, Mean (Range), %			
	Baseline to Day 1	Day 1 to Day 7	Day 7 to Day 28	Baseline to Day 28
Dorzolamide hydrochloride (n = 20)	−21.5 (−37.5 to 10.0)	−6.0 (−40.0 to 40.0)	2.8 (−25.0 to 37.5)	−24.1 (−38.5 to 0.0)
Placebo (n = 20)	0.0 (−30.0 to 42.9)	1.9 (−18.8 to 44.4)	−0.6 (−18.2 to 40.0)	1.3 (−30.0 to 60.0)

Abbreviation: IOP, intraocular pressure.

cision of the measurements in the patients (n=10) and controls (n=10) was 1.7±1.1 µm (range, 0.2-5.0 µm) and 1.0±0.7 µm (range, 0.3-6.0 µm), respectively.

COMMENT

Four-week application of dorzolamide causes a statistically significant thickening of the CCT in patients with cornea guttata. The measurements showed a mean increase of 26.3 µm in CCT in the patients with cornea guttata after 28 days. In the healthy control group, the 4-week application of dorzolamide did not induce significant changes in CCT.

In our previously published study, the mean CCT increase in patients with cornea guttata treated with dorzolamide for 24 hours was 12.0 µm.[18] The difference between our studies might be explained by the lower ECC in patients included in the present study. This group was also more homogeneous concerning the ECC than in the previous study, where the mean ECC was 1321±399 cells/mm² (range, 875-2250 cells/mm²). Comparing the ECCs of the cornea guttata group in the previous study with those in the current study, the unpaired *t* testing showed a significant difference (*P*=.02).

One of the major functions of the endothelial cell layer is continuous fluid secretion. Effected by the cellular electrolyte transport, intercellular fluid transport from the corneal stroma into the aqueous humor is achieved, enabling deturgescence of corneal stroma. This function counterbalances the continuous leak of fluid into the corneal stroma maintained by the imbibition pressure of its glycosaminoglycans. A compromised endothelial cell layer may not execute this function satisfactorily and allow corneal edema, loss of transparency, and impaired vision. As described earlier, CA plays a major role in the bicarbonate pump as it catalyzes hydration and dehydration of carbon dioxide. Because dorzolamide is a potent inhibitor of CA II, concerns have been raised that this drug may have an adverse effect on corneal endothelial cell function by inhibiting the bicarbonate pump.[14] There is evidence against this concern demonstrated by short- and long-term effect studies in which no statistically significant changes in CCT were observed.[11,12,15] Kaminski et al[13] reported minor increases in CCT after 1 day of dorzolamide treatment that were not statistically significant. In contrast, studies showed small but statistically significant changes in long-term[17,21] and short-term[18] use of dorzolamide. All these studies, apart from our previous study, used optical slitlamp pachymetry or conventional ultrasound pachymetry for CCT measurements.

These methods have an unsatisfying reproducibility and yield large deviations because of relatively high interobserver, intraobserver, and interinstrument variability.[22,23] To provide high-precision CCT measurements with low interobserver and intersession variability, the measurements in this study were performed using ACMaster, which is based on the principle of partial coherence interferometry as reported previously.[19,24-26]

To our knowledge, only 1 study[16] described 9 cases of irreversible corneal decompensation after use of dorzolamide. All those patients had a history of previous intraocular surgery (penetrating keratoplasty, cataract surgery, glaucoma surgery). The authors mentioned that dorzolamide may be contraindicated in patients with "borderline" endothelial function because of their capability to attenuate the bicarbonate efflux, which could lead to corneal thickening. In the present study, we included subjects with a compromised endothelial cell layer with low endothelial cell counts (patients with cornea guttata), and we found a statistically significant increase in CCT after 1 day of dorzolamide treatment. This seems to be effected by inhibition of CA in the endothelial cells. During the days that followed, no further significant increase in CCT was detected.

Kuang et al[27] suggested that phosphate might replace bicarbonate as a cotransporter substrate. These endothelial pump mechanisms could create a long-term counterregulatory mechanism to avoid further corneal thickening if the hydrogen carbonate generation via CA is inhibited. Recently, Bonanno[28] discussed a few known and potential fluid transport agonists that might stimulate fluid transport through autocrine pathways. Also the water channel protein AQP1, which is highly expressed in corneal endothelium, might play a role in fluid transport in absence of bicarbonate.[29] One could speculate that a borderline compensated cornea with a severely compromised endothelial cell layer, which under normal conditions already uses all possible mechanisms to guarantee a sufficient deturgescence of the corneal stroma, might decompensate after reduction of bicarbonate transport mechanism caused by dorzolamide therapy. Further studies are needed to evaluate this important topic because Konowal et al[16] reported irreversible corneal decompensation after prolonged use of dorzolamide in patients with seriously compromised corneal endothelium. However, patients in that study might have suffered from an even more significantly inferior condition of corneal endothelium than subjects in the present study, which could account for the different results.

In summary, our study revealed corneal thickening induced by 4-week dorzolamide application in patients

with a compromised corneal endothelial cell layer. The chronic corneal thickening had a mean magnitude of 26 μm (4.7% CCT thickening), which is not clinically relevant. However, this outcome is based on single results of the patients with cornea guttata showing an increase in CCT of up to 14.4%. This is important because a CCT increase of more than 10% may be clinically relevant. Our results indicate that patients with severe cornea guttata or a highly compromised endothelial cell layer might have a higher risk of corneal decompensation after prolonged use of dorzolamide. These findings suggest a more reserved prescription of dorzolamide in patients with cornea guttata and/or low endothelial cell count. Furthermore, we recommend monitoring for patients with borderline compensated corneas or corneas with severe endothelial cell damage who receive dorzolamide therapy.

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