ELSEVIER

Influence of Dorzolamide on Corneal Endothelium

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Purpose: To evaluate the influence of topical 1% dorzolamide treatment for 3 months on the endothelial morphology and the thickness of the cornea.

Methods: The corneal endothelium was investigated in 21 glaucoma patients (29 eyes) who received topical 1% dorzolamide treatment for 3 months. Intraocular pressure, corneal endothelium, and central corneal thickness (CCT) were measured before and 3 months after topical dorzolamide treatment. The relation between the endothelial cell density loss or the CCT increase, and factors such as the history of previous intraocular surgery, the presence of type II diabetes mellitus, type of glaucoma, intraocular pressure before treatment (above or below 20 mm Hg), or the kinds of eye drops used before dorzolamide treatment were evaluated.

Results: The endothelial cell density, coefficient of variation of cell area, and percentage of hexagonal cells did not change significantly. The CCT after treatment (537 ± 34 μm) was significantly increased over that before treatment (530 ± 33 μm). There was no significant relation of endothelial cell loss or CCT increase to any of the above factors.

Conclusions: Topical 1% dorzolamide treatment increases CCT and does not affect corneal endothelial morphology. **Jpn J Ophthalmol 2003;47:129–133** © 2003 Japanese Ophthalmological Society

Key Words: Corneal endothelium, corneal thickness, dorzolamide, glaucoma.

Introduction

Dorzolamide hydrochloride (Trusopt; Merck, Whitehouse Station, NJ, USA) is the first commercially available topical carbonic anhydrase inhibitor. More than 10 kinds of isoenzymes of carbonic anhydrase have been reported in the human eye.[1] Carbonic anhydrase isoenzyme II found primarily in red blood cells also exists in the ciliary processes of the eye.[2] This drug suppresses aqueous humor production by inhibiting the carbonic anhydrase-dependent step of aqueous humor secretion by the ciliary body, resulting in reduced intraocular pressure. Dorzolamide does not show severe systemic adverse reactions such as paresthesia, tinnitus, anorexia, and gastrointestinal disturbances associated with the use of an oral carbonic anhydrase inhibitor (acetazolamide).[3–10]

Besides the ciliary processes, corneal endothelium also possesses the carbonic anhydrase isoenzymes I and II.[2] They play a role in the corneal pumping function, which regulates the flow of water out of the corneal stroma. Carbonic anhydrase inhibitors reduce the corneal pumping function, resulting in increased corneal water content and corneal thickness.[8–11]

There are several reports of increased central corneal thickness (CCT) after topical 2% dorzolamide treatment.[8–11] Kitazawa et al[12] investigated the dose-response relationship of the intraocular pressure-lowering activity of 0.2%, 0.5%, 1%, or 2% dorzolamide. Dorzolamide (0.2%) was less effective than other doses of dorzolamide. Dorzolamide (2%) might be less well tolerated than 0.5% or 1% dorzolamide. Therefore, topical 0.5% and 1% dorzolamide were approved in Japan.

We evaluated the influence of topical 1% dorzolamide treatment for 3 months on the endothelial morphology and the thickness of cornea. There have not been reports of the influence of topical 0.5% or 1% dorzolamide, which are lower concentrations than

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used in previous reports,[8–11] on the endothelial morphology and the thickness of cornea. It is not clear whether these lower concentrations (0.5% and 1%) of dorzolamide treatment will induce changes in corneal endothelial morphology and thickness. We plan further studies on the lower concentration (1%) of dorzolamide and its effects on the cornea.

Materials and Methods

Subjects

We examined 21 glaucoma patients (29 corneas; 6 men and 15 women) at Nadogaya Hospital, Chiba prefecture, between October and December 2001. Mean (± SD) patient age was 71.2 ± 9.3 years (range, 51–84 years). The types of glaucoma included normal tension glaucoma (NTG; 18 eyes), primary open-angle glaucoma (POAG; 10 eyes), and primary angle-closure glaucoma (PACG; 1 eye). The duration of glaucoma was unclear. The anti-glaucomatous eye drops used by the patients before topical dorzolamide treatment had included timolol (4 eyes), carteolol (3 eyes), latanoprost (12 eyes), timolol + latanoprost (5 eyes), timolol + unoprostone (2 eyes), timolol + epinephrine (2 eyes), and carteolol + latanoprost (1 eye). Patients were excluded from this study if they had been previously treated with acetazolamide, had had intraocular surgery during the previous 6 months, or had abnormal cornea.

There were 8 patients (11 eyes) with type II diabetes mellitus. The mean (± SD) duration of diabetes mellitus was 17.0 ± 11.8 years (range, 8–40 years). The hemoglobin A_{1c} was 7.6 ± 0.9% (range, 6.9–9.6%). Ten eyes had a history of previous cataract surgery, of which 9 eyes had phacoemulsification aspiration + intraocular lens implantation and 1 had extracapsular cataract extraction. All patients gave their informed consent for participation in the study.

Methods

The endothelial morphology was quantitated by measuring parameters including cell density, coefficient of variation of cell area, and percentage of hexagonal cells. The central corneal endothelial cells were photographed by specular microscopy, using Noncon Robo CA (Konan Medical, Kobe). Three central cornea microphotographs were taken in each patient and a minimum of 50 cells were counted in each photograph to calculate cell density, coefficient of variation of cell area, and percentage of hexagonal cells. The average of the data in the three microphotographs was used to calculate the measurements for each patient.

CCT was measured with an ultrasonic pachymeter (AL-2000; Tomey, Nagoya) under topical anesthesia. The speed of sound (1640 m/s) was used. The pachymeter tip was placed perpendicularly to the cornea and centered over the undilated pupil. Five consecutive readings were recorded and averaged.

Statistical Analysis

The differences in intraocular pressure, endothelial cell density, coefficient of variation of cell area, percentage of hexagonal cells, and CCT before treatment and 3 months after treatment were analyzed by the paired *t*-test. The changes in endothelial cell density during the 3 months were calculated and analyzed by the independent *t*-test or Mann–Whitney *U*-test in relation to the history of previous cataract surgery, the presence of type II diabetes mellitus, type of glaucoma (NTG and POAG), intraocular pressure before topical dorzolamide treatment (above or below 20 mm Hg), or the kinds of eye drops used before topical dorzolamide treatment.

Results

No severe systemic or ocular adverse effects were induced by the treatment and all patients could continue the topical dorzolamide treatment.

Dorzolamide significantly lowered intraocular pressure from 17.6 ± 3.1 mm Hg (range, 13–26 mm Hg) to 14.2 ± 2.3 mm Hg (range, 11–19 mm Hg) ($P < .001$, paired *t*-test) (Figure 1). The endothelial cell density averaged 2404 ± 352 cells/mm^2 (range, 1684–2956 cells/mm^2) before treatment and 2413 ± 359 cells/mm^2 (range, 1750–3030 cells/mm^2) 3 months after treatment ($P = .82$, paired *t*-test). The coefficient of variation of cell area averaged 0.35 ± 0.05 (range, 0.28–0.46) before treatment and 0.36 ± 0.06 (range, 0.27–0.50) 3 months after treatment ($P = .54$, paired *t*-test). The percentage of hexagonal cells averaged 56.0 ± 7.2% (range, 41.3–68.3%) before treatment and 55.2 ± 9.7% (range, 36.7–72.0%) 3 months after treatment ($P = .65$, paired *t*-test). The CCT averaged 530 ± 33 μm (range, 435–602 μm) before treatment and 537 ± 34 μm (range, 463–599 μm) 3 months after treatment ($P = .02$, paired *t*-test).

During the 3 months of treatment, there was no significant relation between endothelial cell density loss or CCT increase and the history of previous cataract surgery ($P = .17$, $P = .86$, respectively), the presence of type II diabetes mellitus ($P = .31$, $P = .16$, respectively), the type of glaucoma (NTG and POAG) ($P = .73$, $P = .60$, respectively), intraocular pressure before topical dorzolamide treatment (above

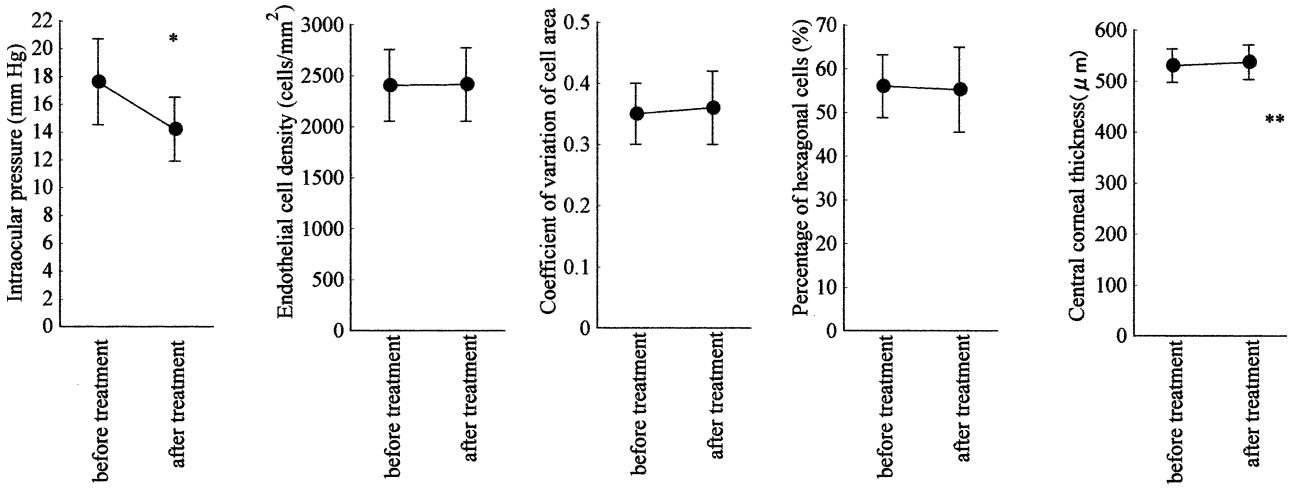

Figure 1. Intraocular pressure, corneal endothelial morphology (endothelial cell density, coefficient of variation of cell area, percentages of hexagonal cells), and central corneal thickness (CCT) before and 3 months after topical 1% dorzolamide treatment (paired *t*-test; $*P < .001$, $**P < .05$)

or below 20 mm Hg) ($P = .29$, $P = .67$, respectively), or the kinds of eye drops used before topical dorzolamide treatment (one or two) ($P = .35$, $P = .26$, respectively) (Table 1).

Discussion

Dorzolamide is clinically effective when used alone or in combination with other topical anti-glaucomatous medications.[3–9,12] The mean decrease of intraocular pressure in patients treated with 2% dorzolamide was reported as 0.6 mm Hg (2.2%) for 6 months,[3] 3.6 mm Hg (13.3%) for 4 weeks,[8] 2.5–3.9 mm Hg (10.6–15.9%) for 14 days,[12] 5.0 mm Hg for 1 year,[4] 15.4% for 24 hours,[5] 4.3–6.2 mm Hg (16.9–22.9%) for 12 months,[6] 4.2 mm Hg (19.6%) for 1 week,[7] and 22% for 90 days.[9] The mean decrease of intraocular pressure in patients treated with 1% dorzolamide was reported as 2.0–4.0 mm Hg (8.6–17.0%) for 14 days.[12] In the current study, 1 patient showed increased intraocular pressure from 13 mm Hg to 19 mm Hg, and the others showed decreased intraocular pressure by 1–10 mm Hg. The mean decrease of intraocular pressure was 3.4 mm Hg (19.3%) for 3 months, which was similar to previous reports.[3–9,12]

In the current study, CCT after 1% dorzolamide treatment was significantly increased over that before treatment. It was not clear which induced increased CCT, the main ingredient of topical dorzolamide, the base dorzolamide mixture, or decreased intraocular pressure. We did not set up any patients as controls. To evaluate rigidly the influences of dorzolamide on corneal endothelium and CCT, patients who showed decreased intraocular pressure without dorzolamide treatment or who were treated with dorzolamide without the main ingredient or without the base mixture, must be set up as controls. It was, however, clinically difficult to use any patients as controls.

There are some reports of increased CCT after 2% dorzolamide treatment[8,10,11] as well as several reports of unchanged CCT after the same treatment.[3–5,9] Herndon et al[10] reported that those eyes with glaucoma being treated with topical dorzolamide hydrochloride had a significantly increased CCT (0.560 ± 0.025 mm) compared with those eyes with glaucoma not being treated with dorzolamide (0.551 ± 0.020 mm). Wilkerson et al[8] investigated the safety and efficacy of 2% dorzolamide in a 4-week, double-masked, randomized, placebo-controlled trial. They reported mean corneal thickness was slightly increased for the dorzolamide-treated group compared with the placebo-treated group (0.009 mm vs. 0.001 mm, respectively, $P < .05$), and the change in endothelial cell counts was similar ($P > .25$). Egan et al[5] reported no significant increase of CCT in healthy eyes that received 2% dorzolamide compared with those that received placebo. Lass et al[3] reported that the mean percent loss in endothelial cell density was 3.6% and the mean percent change for corneal thickness was 0.47% after 1 year of topical 2% dorzolamide treatment. Dorzolamide was equivalent to timolol and betaxolol in terms of the change in corneal endothelial cell density and thickness. Kaminski et al[9] reported that in patients treated with 2% dorzolamide,

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Table 1. The Relation Between Endothelial Cell Density Loss or Central Corneal Thickness (CCT) Increase, and Various Factors

Factor*	N	Endothelial Cell Density Loss (%)	*P*	CCT Increase (%)	*P*
History of previous cataract surgery					
(+)	10	2.4 ± 6.5	0.17†	1.3 ± 3.7	0.86†
(−)	19	−2.4 ± 9.5		1.5 ± 2.9	
Presence of type II diabetes mellitus					
(+)	11	−2.8 ± 9.3	0.31†	0.2 ± 1.8	0.16‡
(−)	18	0.6 ± 8.5		2.2 ± 3.5	
Type of glaucoma					
NTG	18	−0.6 ± 9.0	0.73†	1.8 ± 3.2	0.60†
POAG	10	−1.8 ± 8.7		1.1 ± 3.1	
Intraocular pressure before treatment					
≥20 mm Hg	9	−3.3 ± 6.9	0.29†	1.1 ± 3.4	0.67†
<20 mm Hg	20	5.0 ± 9.4		1.6 ± 3.1	
Kinds of eye drops before treatment					
One	19	0.4 ± 9.9	0.35†	1.0 ± 2.6	0.26†
Two	10	−2.8 ± 6.1		2.4 ± 3.9	

*NTG: normal-tension glaucoma, POAG: primary open-angle glaucoma.
†Independent *t*-test.
‡Mann–Whitney *U*-test.

mean corneal thickness was slightly increased on day 1 (statistically not significant) and returned to baseline measurements at the following visits, and endothelial cell count showed no change. Giasson et al[4] reported that patients followed up after 1 year of 2% dorzolamide use did not differ significantly in values of endothelial cell density and corneal thickness compared with controls.

There are no reports of decreased endothelial cell density after topical 2% dorzolamide treatment. There are several reports of unchanged endothelial cell density after this treatment.[3–5,8,9] In the current study, the endothelial cell density 3 months after 1% dorzolamide treatment was similar to that before treatment. There are, however, two cases that showed more than a 10% decrease of endothelial cell density 3 months after treatment. One case, a patient who was 73 years old, was diagnosed with NTG, had diabetes mellitus, and had undergone cataract surgery 1 year before. The other was 84 years old, the oldest in the current study; he was diagnosed as having POAG, did not have diabetes mellitus, and had not undergone any ocular surgery previously. The endothelial cell density before treatment was 2251 cells/mm^2 and 2916 cells/mm^2, respectively. These two patients had been treated with only latanoprost previously. When these 2 of 12 patients (16.6%) who were treated with only latanoprost previously showed more than a 10% decrease in endothelial cell density 3 months after topical 1% dorzolamide treatment in the current study, we thought the risk factors might have been the combination of using latanoprost and the older patient age, or using latanoprost, previous cataract surgery, and type II diabetes mellitus. We should use topical 1% dorzolamide carefully for corneal endothelium and evaluate the corneal endothelial cell density every 3 months. On the other hand, there were no cases that showed more than a 10% increase of CCT 3 months after treatment.

In the current study, we evaluated the influence of not 2% but 1% dorzolamide on corneal endothelium and CCT. The factors for each patient were analyzed before and 3 months after treatment. There are some reports that compared corneal endothelial cell density and CCT before and after 2% dorzolamide treatment in each patient.[8,9] In the current study, CCT was increased by 7 μm, which was similar to a previous report (9 μm).[8] There were no changes in the endothelial cell density, which was also similar to previous reports.[8,9]

In the current study, there was no significant relation between endothelial cell density loss or CCT increase and the history of previous cataract surgery, the presence of type II diabetes mellitus, the type of glaucoma (NTG and POAG), intraocular pressure before topical dorzolamide treatment (above or below 20 mm Hg), or the kinds of eye drops used before topical dorzolamide treatment. We could not find any risk factors for endothelial cell loss or increased CCT in patients with dorzolamide treatment. To evaluate rigidly the relation of endothelial

cell density loss or CCT increase to the above factors, we must analyze these by multiple regression analysis. The subjects were too few in the current study to use multiple regression analysis, and these factors were analyzed individually. Konowal et al[11] reported 9 cases of overt corneal decompensation (irreversible corneal edema) after starting topical 2% dorzolamide treatment. They, however, did not evaluate CCT. Those patients all had histories of previous intraocular surgery (cataract surgery, trabeculectomy, or penetrating keratoplasty) and therefore had compromised corneas.

Although a statistically significant increase of CCT was found 3 months after even topical 1% dorzolamide treatment, it is not known if this difference is clinically significant. Corneal endothelial cell density, the coefficient of variation of the cell area, and the percentage of hexagonal cells had not worsened 3 months after topical 1% dorzolamide treatment in the current study. The influence on the endothelial morphology and the thickness of cornea after the lower concentration (1%) dorzolamide treatment might be as severe as after 2% dorzolamide treatment. We will next evaluate the influence on the endothelial morphology and the thickness of cornea after a much lower concentration (0.5%) dorzolamide treatment. As the follow-up period was too short in the current study to evaluate the influence of topical 1% dorzolamide treatment on the endothelial morphology and corneal thickness, we should also carefully observe the effect on the corneal endothelium in patients treated with topical 1% dorzolamide.

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