Effect of Dexamethasone on Corneal Endothelial Function in Fuchs’ Dystrophy

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Thirteen patients with Fuchs’ endothelial dystrophy were studied to measure the potential effects of topically applied dexamethasone on endothelial function. Endothelial permeability in the Fuchs’ dystrophy patients was not different from that found in normal controls. One eye, chosen at random, was treated topically four times a day for 7 days with 0.1% dexamethasone phosphate. The contralateral eye was treated with a placebo of identical appearance. Prior to treatment, there were no statistically significant differences in the means of the intraocular pressure, corneal thickness, endothelial permeability, or endothelial pump rate between the dexamethasone- and placebo-treated groups. In the placebo-treated eyes, a significant decrease was observed in both endothelial permeability and endothelial pump rate over the course of the study. No statistically significant changes occurred in the dexamethasone-treated eyes over the same period. When the dexamethasone group was compared with the placebo group, there was a significant difference in the change in endothelial pump rate between the two groups, attributable in large part to the decrease in pump rate observed in the placebo group over the course of treatment. We interpret our data as lacking support for the concept that topical steroids are beneficial for the treatment of stromal edema in patients with Fuchs’ dystrophy.


Fuchs’ endothelial dystrophy is a disease of unknown etiology resulting in damage to the corneal endothelium leading sometimes to vision-compromising corneal edema. Previous studies have suggested that the earliest defect in Fuchs’ dystrophy is a breakdown in corneal endothelial barrier function resulting in increased permeability.1

It is hypothesized on the basis of empirical observations that topical corticosteroids have a beneficial effect on stromal edema in some patients with Fuchs’ dystrophy.2 Several studies have been conducted to measure the effect of topical steroids in normal eyes. Baum et al3 found a small but significant increase in corneal thickness in 35% of normal eyes treated for 4 weeks with 0.1% dexamethasone phosphate. The effect was especially pronounced in four persons who were intraocular pressure “high responders” to steroids. Twelve patients in Baum’s study with mild to moderate cornea guttata did not differ from normals in their response to dexamethasone phosphate. Rice et al4 found no significant change in corneal thickness or endothelial permeability in 24 normal subjects treated for 1 week with topical 0.1% dexamethasone.

Several studies have investigated the effect of topical corticosteroids on endothelial cell function in rabbits. In a study of normal rabbits, Hara5 observed a decrease in corneal thickness after topical hydrocortisone treatment. Hara hypothesized that the decrease might be attributed to a reduced rate of fluid imbibition, to an increased rate of evaporation, or to increased endothelial pump activity. Kikkawa6 described a thinning of the cornea in rabbits in response to intravenous or subconjunctival hydrocortisone. Stevens et al7 reported that topical 1% prednisolone acetate stimulated endothelial pump function in mature pigmented rabbits with central endothelial cryoinjury. After applying 3H-dexamethasone topically to rabbit eyes, Hernandez et al9 found the labeled drug concentrated in corneal epithelial cells and kerocytes, but not in endothelial cells. An accumulation of label between the corneal stroma and Descemet’s membrane suggested that this membrane acts as a partial barrier to posterior diffusion of the drug. This study does not exclude the possibility of corticosteroid receptors being located in the corneal endothelial cells. (Only a single application of dexamethasone was used in these experiments; it is possible that endothelial localization would have been detected with repeated applications.) It is not known how these results relate to the hypothetical benefit of corticoste-
For this reason, we undertook to investigate the effect of topical dexamethasone on endothelial permeability, endothelial pump rate and corneal thickness in patients with mild stromal edema from Fuchs' dystrophy.

Materials and Methods

Thirteen patients with Fuchs' dystrophy who met the following criteria were asked to participate in the study. All subjects had bilateral cornea guttata (three with grade 3 and ten with grade 4 bilaterally) with clear corneal stroma and no epithelial edema. In the grading scale used, grade 1 was minimal guttae and grade 4 was central confluence. We chose patients with relatively equal involvement in the two eyes. All participants had an initial intraocular pressure in the two eyes of less than or equal to 18 mm Hg. No patient had extracocular or intraocular inflammation (no conjunctival injection, no inflammatory cells in the cornea by slit lamp examination, and less than one cell per 1 x 2 mm slit lamp beam in the anterior chamber). Subjects had no ocular medicines or oral carbonic anhydrase inhibitors or anti-inflammatory medications for at least 2 weeks prior to the start of the study. No patient had ocular abnormalities other than cataract, and none had previous intraocular surgery. Four patients were male and nine were female. Informed consent was obtained from all subjects prior to enrollment in the study.

On their first day in the study all patients had complete ocular histories taken and physical examinations performed including slit lamp biomicroscopy, Hruby lens examination, indirect ophthalmoscopy, and Goldmann tonometry. Background fluorescence was measured with a two-dimensional scanning fluorophotometer. Each patient was provided with an understandable instruction sheet, including a log requiring an entry after the administration of each medication. The patient was given a 2 ml plastic vial of 2% fluorescein.

At 4:00 AM on the next day (day 0), the patient administered one drop of 2% fluorescein in both eyes and followed this with a second drop 5 min later. Instructions were given for removing excess fluorescein from the eyelids with moist cotton. The patient then returned to sleep for several hours. At 10 AM, 11 AM, 12 noon, 1 PM, and 2 PM, the concentrations of fluorescein in the corneal stroma and the anterior chamber were measured in each eye with the fluorophotometer. Between measurements, the subject was permitted to sit, read or walk about ad libitum. Each patient was instructed to refrain from drinking alcohol or large volumes of water, using any drugs or eating large meals, any of which might introduce unwanted fluctuations in the flow of aqueous humor. The volume of the corneal stroma was assumed to be 70 µl. The volume of the anterior chamber was determined from a Zeiss slit lamp photograph. The central corneal thickness was measured with a Heer-Schulte specular microscope (Product Research Organization, Inc., Tustin, CA). Each patient was then given two identical dropper bottles labelled A and B. One of the two randomly determined bottles contained 0.1% dexamethasone phosphate (Decadron®, Merck, Sharp and Dohme, West Point, PA) and the other contained the vehicle of Decadron. The eye to receive the 0.1% dexamethasone phosphate was known neither to the patient nor to the examiner until all data were collected. The patient was instructed that solution A was to be administered to the right eye and solution B to the left eye. Each patient was given a log in which to record each instillation.

On days 1 through 7, the subjects were instructed to apply single drops of solutions A and B four times a day (8 AM, 12 noon, 4 PM, and 8 PM) and to record each administration in the log. At 4:00 AM on day 8, the patient again applied one 2% fluorescein drop to each eye, followed 5 min later by a second drop. At 8 AM the subjects applied the last dose of Decadron and vehicle. Fluorophotometric measurements were repeated at 10 AM, 11 AM, 12 noon, 1 PM, and 2 PM. Intraocular pressure was measured afterward with a Goldmann tonometer, and central corneal thickness measurements were repeated. Unused drops and logs were collected from each subject in order to assess compliance.

Six of the 13 patients had follow-up measurements of endothelial permeability performed by the same method 8 to 10 months after day 8. Endothelial permeability to fluorescein was calculated from the rate of disappearance of fluorescein from the cornea and the gradient between the stroma and the anterior chamber. The concentration of fluorescein in the stroma at any time was determined from the least squares linear fit to the logarithm of the stromal measurements versus time. This data-smoothing technique was used to reduce random fluctuations in the measurements of stromal fluorescence. The cornea-to-anterior chamber mass transfer coefficient ($k_{c,a}$) was calculated for each pair of hourly measurements from the following equation, derived from those of Jones and Maurice:

$$k_{c,a} = \frac{\Delta C_c}{(r_cC_a - C_c)\Delta t}$$

where $C_a$ is the instantaneous concentration of fluorescein in the anterior chamber (measured), $C_c$ is the instantaneous concentration of fluorescein in the stroma (determined from the best-fitting line), $C_a$ and $C_c$ are the concentrations in the anterior chamber and corneal stroma, respectively, $r_c$ is the corneal-to-ACh transfer coefficient, and $\Delta t$ is the time interval between measurements.
Table 1. Measured variables before treatment*

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Intraocular pressure, mm Hg</th>
<th>Corneal thickness, mm</th>
<th>Endothelial permeability, $\times 10^{-4}$ cm/min</th>
<th>Endothelial pump rate, mm Hg $\times L_p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>13</td>
<td>13.7 ± 2.0</td>
<td>0.61 ± 0.04</td>
<td>4.14 ± 1.08</td>
<td>35.3 ± 11.6</td>
</tr>
<tr>
<td>Placebo</td>
<td>13</td>
<td>13.9 ± 2.3</td>
<td>0.61 ± 0.04</td>
<td>4.85 ± 1.61</td>
<td>42.1 ± 13.1</td>
</tr>
</tbody>
</table>

* Mean ± standard deviation on day 0.

$\tilde{C}_a$ are the average concentrations of fluorescein in the stroma and anterior chamber during the time interval, $t = 1$ to $t = 2$, calculated on the assumption that the loss of dye is a first order process:

$$\tilde{C} = \frac{C_1 - C_2}{\ln (C_1/C_2)}$$

t is time, and $r_{ca}$ is the stroma/anterior chamber distribution ratio of fluorescein at equilibrium, assumed to be 1.6 in humans.

Endothelial permeability to fluorescein in cm/min was calculated as follows:

$$\text{permeability} = k_{ca} \times CT \times r_{ca}$$

where $k_{ca}$ is the mean of the values calculated for each of the four hourly intervals and CT is the central corneal thickness as measured with the specular microscope.

The endothelial pump rate was calculated using the relationship derived by Burns et al., assuming that the swelling pressure-hydration-thickness relationship was normal:

$$\text{Endothelial pump rate} = 1310(0.942 - CT)^{3.275}(P/P_n)L_p$$

where CT is central corneal thickness in mm as measured with the specular microscope, $P$ is the measured permeability to fluorescein, $P_n$ is the normal permeability to fluorescein measured by the same technique in 80 normal subjects aged 5 to 79 years and found to be $4.03 \times 10^{-4}$ cm/min, and $L_p$ is the normal hydraulic conductivity of the endothelium in rate/mm Hg. The pump rate is expressed as a factor times the hydraulic conductivity because $L_p$ is not accurately known in humans.

A paired student t-test was used to make statistical comparisons; $P < 0.05$ was considered statistically significant.

Results

The average age for the 13 patients enrolled in the study, all of whom met the specified criteria, was 58.3 ± 15.8 (standard deviation) years (range 20-83 years). There were no statistically significant differences in the means of the intraocular pressure, corneal thickness, endothelial permeability or endothelial pump rate between the dexamethasone and placebo groups on day 0 of the study (Table 1).

Logs maintained by the patients with Fuchs’ dystrophy during the course of the study demonstrated 100% compliance in the administration of the dexamethasone and placebo by each subject.

No significant differences were found between day 0 and day 8 in the means of the measured variables for the dexamethasone-treated eyes. There was, however, a significant decrease between day 0 and day 8 in the endothelial permeability and the endothelial pump rate in the placebo group (Table 2).

When the changes in the measured variables in the dexamethasone group were compared to those in the placebo group, a statistically significant difference was found only in the change in endothelial pump rate (Table 2).

As discussed in Lachin, a study such as this would find a statistically significant decrease in endothelial permeability after treatment 90% of the time if the true decrease in permeability were at least 15% or $0.75 \times 10^{-4}$ cm/min (single-sided paired analysis, $\alpha = 0.05$, $\beta = 0.10$). Therefore, we can be 90% certain that endothelial permeability in eyes with Fuchs’ dystrophy is not decreased 15% or more by topical 0.1% dexamethasone four times daily. Similarly, a true decrease in corneal thickness of 2% (0.01 mm) would have been detected with 90% certainty.

Six of the 13 patients in the study had measurements of endothelial permeability performed eight to ten months after day 8. The mean change in endothelial permeability from day 8 to the followup measurement was $+0.84 \pm 1.56 \times 10^{-4}$ cm/min in the six dexamethasone-treated eyes and $+0.67 \pm 1.57 \times 10^{-4}$ cm/min in the six placebo-treated eyes.

Discussion

The purpose of this study was to investigate in a controlled experiment whether topical steroids may have a measurable and possibly beneficial effect on the corneas of patients with Fuchs’ dystrophy. No significant change was found in the dexamethasone-treated eyes from day 0 to day 8 in intraocular pressure, corneal thickness, endothelial permeability or endothelial pump rate after 7 days of topical steroid treatment. In the placebo-treated eyes, a significant decrease in both endothelial permeability and endothelial pump rate was found after 7 days of topical...
Table 2. Changes after treatment

<table>
<thead>
<tr>
<th></th>
<th>Dexamethasone</th>
<th>Placebo</th>
<th>Change with dexamethasone versus change with placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 8–Day 0*</td>
<td>P†</td>
<td>Day 8–Day 0*</td>
</tr>
<tr>
<td>Intraocular pressure, mm Hg</td>
<td>+0.8 ± 1.8</td>
<td>0.14</td>
<td>+0.6 ± 2.1</td>
</tr>
<tr>
<td>Corneal thickness, mm</td>
<td>−0.007 ± 0.014</td>
<td>0.10</td>
<td>−0.002 ± 0.013</td>
</tr>
<tr>
<td>Endothelial permeability,</td>
<td>+0.18 ± 0.95</td>
<td>0.50</td>
<td>−0.67 ± 0.92</td>
</tr>
<tr>
<td>X 10^{-4} cm/min</td>
<td>+5.1 ± 13.2</td>
<td>0.19</td>
<td>−4.8 ± 7.0</td>
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* Mean difference ± standard deviation of the differences.
† P value for two-sided paired t-test.

placebo. This change in the placebo-treated eyes has no obvious explanation. It could have been due to chance, due to a systematic error or due to one or more of the components of the placebo drops. There is a 5% chance that the observed placebo effect would have been detected when in fact there was no effect (alpha error).

Although differences in endothelial permeability and endothelial pump rate between the two groups before treatment are not statistically significant (Table 1), the changes noted from day 0 to day 8 (Table 2) further diminish these differences. Because patients with relatively equal disease in both eyes were selected for the study, this might be expected to occur by chance if the dexamethasone and placebo in fact had no effect. Furthermore, the increase in average endothelial permeability noted in both the dexamethasone- and placebo-treated eyes for patients who had follow-up studies off treatment also suggests that the change noted in the placebo-treated eyes occurred by chance. If the observed decrease in average endothelial permeability with placebo treatment were real, then an increase would have been expected after the washout period. However, since an even greater increase was observed in the sterile-treated eyes after a washout period, a chance variation in the baseline over time is suggested. This finding also suggests that the significant decrease in the calculated pump rate in, the placebo-treated eyes also occurred by chance, since the calculated pump rate is directly proportional to the measured endothelial permeability.

Bisulfite and benzalkonium chloride, two of the components of the placebo drops have been shown to cause an increase in endothelial permeability if they come in direct contact with the endothelium. Therefore, it seems unlikely that these components would be responsible for the observed decrease. It is noteworthy that no significant change in endothelial permeability was found in a group receiving the identical placebo solution in a previous study.4

Burns et al,1 using the slit lamp fluorophotometer, reported an increase in endothelial permeability in Fuchs’ dystrophy patients compared with normal controls. In the present study, endothelial permeability measured with a more precise two-dimensional scanning fluorophotometer was not statistically different in Fuchs’ dystrophy patients compared to normal subjects. We have recently confirmed this finding with an additional study of 26 patients with Fuchs’ dystrophy and increased corneal thickness and 41 age-matched controls. Therefore, the hypothesis of Burns et al,1 that increased endothelial permeability is the earliest defect in Fuchs’ dystrophy, may be incorrect. In addition, this study has not ruled out the unlikely possibility that steroid treatment could be beneficial in patients with more severe Fuchs’ dystrophy in whom endothelial permeability is increased.

Previous work using the rabbit model has demonstrated a decrease in corneal thickness in response to topical, subconjunctival or intravenous steroids.5,6 Stevens et al18 have reported a steroid-induced stimulation of endothelial pump function in rabbits with central endothelial cryoinjury. Absence of an effect by dexamethasone on endothelial pump function in the present study suggests that the response of diseased human corneal endothelium to topical steroids differs from that in the rabbit. Previous work by Rice et al4 demonstrated that barrier and pump function in normal human corneal endothelium is also unresponsive to topical steroids.

Despite the ambiguity about the interpretation of the results of the placebo group of eyes, no evidence has been found that a week’s treatment with a potent topical steroid improves the barrier or the pumping functions of the endothelium in Fuchs’ dystrophy. These results lend no support to the idea that steroids would hasten deturgescence of the cornea in such patients.

Key words: Fuchs’ dystrophy, endothelium, endothelial permeability, endothelial pump function, corneal thickness, corticosteroid
Acknowledgment

The authors thank Merck, Sharp and Dohme Research Laboratories, West Point, Pennsylvania, for providing the dexamethasone and placebo solutions.

References