Acute Effect of Thymoxamine on Aqueous Humor Formation in the Epinephrine-treated Normal Eye as Measured by Fluorophotometry

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The acute effect of 0.5% thymoxamine and 1% epinephrine on aqueous humor flow was evaluated by fluorophotometry in 25 normal human subjects in a randomized, double-blind, placebo-controlled study. Changes in intraocular pressure, anterior chamber volume, and pupil diameter were also measured. The results of this study indicate that epinephrine alone increases aqueous humor flow by 19% and that thymoxamine in a dose sufficient to produce miosis does not alter this acute effect of epinephrine. Invest Ophthalmol Vis Sci 24:165-168, 1983

Epinephrine, an alpha and beta adrenergic agonist, is an effective topical ocular hypotensive agent commonly used in the treatment of glaucoma. Three fluorophotometric studies have demonstrated that epinephrine diminishes the rate of aqueous humor formation in the human eye.1-3 Three other recent studies of the rate of clearance of topically applied fluorescein suggest that epinephrine acutely increases rather than decreases the rate of flow of aqueous humor through the anterior chamber.4-6 This discrepancy may be due to time-dependent or dose-dependent effects of epinephrine. One study found the effect of epinephrine on aqueous humor flow to be so small and so variable from one subject to another that no time-dependent effect was discernable.6

To determine whether the variability of epinephrine's effect on aqueous flow is due to its mixed alpha and beta agonism, this effect was examined in the presence of alpha blockade with thymoxamine. Topical application of this drug has been shown to produce miosis without affecting intraocular pressure, tonographic facility of outflow, or the rate of aqueous humor formation.7-8 The effect of epinephrine alone and the effect of epinephrine combined with thymoxamine on the rate of aqueous flow in the normal human eye is reported.

Materials and Methods

The same subjects who participated in the previous study of Lee and Brubaker8 on the effect of thymoxamine and the same drug/placebo sequence were used.8 The present study was performed 4 weeks after the previous study. These 12 men and 13 women had healthy eyes by routine examination and intraocular pressures differing by 3 mmHg or less. Thymoxamine hydrochloride, 0.5% ophthalmic solution (IND number 17,002), and an identical-appearing placebo vehicle solution were instilled into one test and one control eye of each subject. Fifteen minutes later a commercially prepared solution of 1% epinephrine hydrochloride (Epifrin; Allergan Pharmaceuticals, Irvine, CA) was instilled into both eyes. The eye to be treated with thymoxamine was chosen randomly, and its identity kept from both subjects and examiners.

Pupillary response, anterior chamber volume, and intraocular pressure were measured in the same sequence and fashion as in the earlier study on thymoxamine vs placebo by Lee and Brubaker.8 Thirty minutes after treatment the apparent fluorescence of the eye was measured using the fluorophotometer described by Brubaker and Coakes.9 Corneal fluorescein iontophoresis was then performed with an electrode of 10% fluorescein and 2% agar. The intensity of separate and combined corneal and anterior chamber fluorescence were measured 30 min, 2 hrs, and 7 hrs after iontophoresis. The thymoxamine and pla-
Table 1. Summary of data and statistical analysis

<table>
<thead>
<tr>
<th></th>
<th>Previous study</th>
<th>Present study</th>
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<tbody>
<tr>
<td></td>
<td>Group P† Placebo</td>
<td>Group T† Thymoxamine</td>
</tr>
<tr>
<td>Intraocular pressure, mmHg</td>
<td>12.4 ± 2.6</td>
<td>12.6 ± 2.5</td>
</tr>
<tr>
<td>Morning, before drug</td>
<td>11.6 ± 2.1</td>
<td>11.4 ± 2.0</td>
</tr>
<tr>
<td>Afternoon, after drug</td>
<td>11.6 ± 2.1</td>
<td>11.4 ± 2.0</td>
</tr>
<tr>
<td>Anterior chamber volume, µl</td>
<td>199 ± 39</td>
<td>195 ± 34</td>
</tr>
<tr>
<td>Morning, before drug</td>
<td>199 ± 36</td>
<td>193 ± 32</td>
</tr>
<tr>
<td>Afternoon, after drug</td>
<td>199 ± 36</td>
<td>193 ± 32</td>
</tr>
<tr>
<td>Cornea-to-anterior chamber transfer coefficient, min⁻¹ X 10⁻³</td>
<td>2.3 ± 1.2</td>
<td>2.5 ± 1.1</td>
</tr>
<tr>
<td>Anterior chamber elimination coefficient, min⁻¹ X 10⁻²</td>
<td>1.34 ± 0.34</td>
<td>1.45 ± 0.38</td>
</tr>
<tr>
<td>Aqueous humor flow, µl/min</td>
<td>2.35 ± 0.61</td>
<td>2.48 ± 0.62</td>
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* Statistically significant.

cebo drops were repeated 2 hrs after iontophoresis, and the epinephrine drops were repeated several minutes after those drops.

The cornea-to-anterior chamber transfer coefficient for fluorescein (KCa) and the anterior chamber elimination coefficient (Ka) were determined by the nomographic method of Coakes and Brubaker. The cornea-to-anterior chamber transfer coefficient for fluorescein (KCa) and the anterior chamber elimination coefficient (Ka) were determined by the nomographic method of Coakes and Brubaker.10 Pupillography was used to determine the effects of epinephrine and thymoxamine on the pupil.

Results of the treated and untreated eye of each subject were compared by two-sided tests, and a probability of 0.05 or less was considered statistically significant. For paired data, the t-test for paired samples and the paired Wilcoxon tests were used. The coefficients of variation between right and left eyes for flow and for Kca were determined by the same methods used in a group of 30 normal subjects who received no drug in either eye.13 These coefficients were used to determine the smallest detectable drug effect with the sample studied. This calculation was made with the method of Cochran and Cox11 using a statistical power of 0.8.

Results

Eyes treated with placebo plus epinephrine will be referred to as the P-E group, and eyes treated with thymoxamine plus epinephrine will be referred to as the T-E group. The results are summarized in Table 1.

Intraocular pressure in the P-E eyes was 12.4 ± 2.6 mmHg (mean ± SD) before treatment, and 10.9 ± 2.3 mmHg at its completion. Intraocular pressure in the T-E eyes was 12.6 ± 2.5 mmHg before treatment and 10.6 ± 2.3 mmHg after treatment. No statistically significant difference was observed in the intraocular pressures between the two groups of eyes either before or after administration of the drugs. The anterior chamber volume of the P-E eyes before application of any drug was 196 ± 38 µl and 194 ± 35 µl in the T-E eyes. There was no statistically significant change in anterior chamber volume in either group after drug application. The cornea-to-anterior chamber transfer coefficient for fluorescein in the P-E eyes was 3.0 ± 1.1 X 10⁻³ min⁻¹, and 3.0 ± 1.0 X 10⁻³ min⁻¹ in the T-E eyes. The anterior chamber elimination coefficient for fluorescein was 1.5 ± 0.4 X 10⁻² min⁻¹ for the P-E eyes and 1.7 ± 0.4 X 10⁻² min⁻¹ for the T-E eyes, and this difference was not statistically significant. The rate of aqueous flow was calculated from the anterior chamber volume and the anterior chamber elimination coefficient. The rate of flow was 2.66 ± 0.5 µl/min in the P-E eyes and 2.74 ± 0.5 µl/min in the T-E eyes. This small difference was not statistically significant.

The drug effects in the P-E eyes and the T-E eyes were compared to those of thymoxamine and placebo alone in the same subjects. The placebo-treated eyes are designated group P and the thymoxamine treated eyes as group T. Table 1 also compares the data from the present experiment to those of the previous experiment. Statistical comparison of the four groups of eyes suggested that epinephrine increased the cornea-to-anterior chamber transfer coefficient by 20 to 30%, and the rate of aqueous flow by 10 to 20%. Thymoxamine, either alone or with epinephrine, had no statistically significant effect on either of these measures.
Thymoxamine caused miosis in the normal human eye treated with epinephrine. Table 2 outlines the means and standard deviations of pupillary response to 1% epinephrine and to 0.5% thymoxamine and 1% epinephrine. Pupillary response was measured as the difference between pretreatment and posttreatment pupillary diameters. The difference in pupillary response of P-E and T-E eyes was statistically significant in the dark, as well as following a light and sound stimulus.

Discussion

This study suggests that thymoxamine does not alter the acute effect of epinephrine on aqueous humor flow. Compared to placebo, epinephrine alone increases aqueous humor flow by 19%, and the cornea-to-anterior chamber transfer coefficient by 30%. The former effect has been noted in previous studies using the same techniques as used here, but the latter effect was not seen in any of these previous studies. The effect of epinephrine on the cornea-to-anterior chamber transfer coefficient in epinephrine-treated eyes does not affect the measurement of the anterior chamber elimination coefficient or the calculation of aqueous humor flow since these two variables are measured independently. Neither of these effects of epinephrine appeared to be altered by thymoxamine. It is possible that the concentration of thymoxamine required to block all of the alpha-adrenergic effects of epinephrine exceeds that required to produce miosis in the epinephrine treated eye (12) (see Table 2). At any rate, thymoxamine in a concentration high enough to produce miosis causes no measurable change in the effect of epinephrine on flow.

It is possible that thymoxamine's effect on aqueous flow may have been missed because of the variability of flow as measured by this technique, and also because of the variability of flow between the right and left eyes of normal subjects. The same measurement was made in both eyes of 30 normal untreated subjects. No significant differences were found between the two eyes, and the standard deviation of the differences in flow between the eyes was found to be 20% of the mean flow. With a sample size of 25 a drug effect of 17% or greater would have been detectable. Smaller drug effects could have been missed because of naturally occurring variability in flow between two fellow eyes and the limited precision of the technique to measure flow.

A study of Townsend and Brubaker indicated that the acute effect of epinephrine was to increase the rate of aqueous humor formation and to decrease intraocular pressure. The decrease in intraocular pres-
sure was assumed to be due to an increase in the pressure insensitive outflow, and an increase in the tonographic C value. Wand and Grant\(^7\) did not demonstrate a significant effect of thymoxamine on intraocular pressure or facility of outflow. Lee and Brubaker\(^8\) also failed to detect a significant effect of thymoxamine on the rate of aqueous humor formation. Thymoxamine in the dosage used in this study may not have blocked all of the alpha-adrenergic effects of epinephrine, but it did not block the flow stimulating effect of epinephrine. We doubt that the flow stimulating property of epinephrine is alpha mediated but do not know specifically how it is mediated.

In vitro studies using isolated preparations of canine saphenous and portal mesenteric veins have shown that thymoxamine acts mainly on post-junctional alpha\(_2\)-adrenergic receptors.\(^{12}\) Interestingly, prazosin, another postsynaptic alpha\(_1\)-adrenergic blocker, has been shown to cause a decrease in intraocular pressure independent of a decrease in systemic blood pressure in rabbits.\(^{14-16}\) This suggests that topical prazosin may merit investigation as an ocular hypotensive agent for human beings.

Key words: thymoxamine, epinephrine, fluorophotometry, aqueous humor flow, normal human eyes.

References