Effect of 8-iso Prostaglandin E₂ on Aqueous Humor Dynamics in Monkeys

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Objective: To evaluate the effects of 8-iso prostaglandin E₂ (8-iso PGE₂; prosta-5,13-dien-1-oic acid, 11,15-dihydroxy-9-oxo-,[5Z,8β-11X,13E,15δ]-) on the intraocular pressure (IOP), outflow facility, and aqueous humor flow rates in normal monkeys and monkeys with glaucoma.

Methods: The IOP was measured before and as long as 6 hours after the topical application of 8-iso PGE₂ to 1 eye of 6 normal monkeys and to the glaucomatous eye of 8 monkeys with unilateral laser-induced glaucoma. The pupil diameter was measured at the same times as the IOP measurements in the normal monkeys. Topographic outflow facility and fluorophotometric flow rates of aqueous humor were measured in 6 normal monkeys before and after drug treatment.

Results: In normal monkeys, a single dose of 0.1% 8-iso PGE₂ reduced (P<.01) the IOP for 4 hours in the treated eyes with a maximum (mean ± SEM) reduction of 3.2 ± 0.2 mm Hg, compared with the contralateral control eyes. The pupil size was smaller (P<.01) in the treated eyes by as much as 1.0 ± 0.2 mm for 4 hours. In 8 glaucomatous monkey eyes, the application of 0.05% and 0.1% 8-iso PGE₂ reduced the IOP (P<.01) for as long as 2 and 5 hours, respectively. The maximum reduction in the IOP was 4.6 ± 0.8 mm Hg (0.05%) and 6.0 ± 0.8 mm Hg (0.1%) compared with baseline measurements. The magnitude and duration of the ocular hypotensive effect were enhanced with twice-a-day administration for 5 consecutive days. Outflow facility in normal monkey eyes was increased (P<.05) by 48% in the treated eyes, and aqueous humor flow was unchanged (P>.10), compared with vehicle-treated contralateral control eyes. Mild eyelid edema, conjunctival edema, hyperemia, and discharge appeared in some eyes treated with the 0.1% drug concentration.

Conclusions: The use of 8-iso PGE₂ reduces the IOP in both normal and glaucomatous monkey eyes. An increase in outflow facility appears to account for most of the IOP reduction in normal monkeys.

Clinical Relevance: The application of 8-iso PGE₂ may have potential for the treatment of glaucoma as an outflow facility–increasing drug.


RESULTS

The unilateral topical application of 0.1% 8-iso PGE₂ to the eyes of 6 normal monkeys reduced (P<.01) the IOP for 4 hours in the treated eyes. The maximum difference in IOP between treated eyes and contralateral control eyes was 3.2 ± 0.2 mm Hg (Figure 1). The pupil size was smaller (P<.01) in the treated eyes than in the contralateral control eyes by as much as 1.0 ± 0.2 mm for 4 hours following treatment (Figure 2). Mild eyelid edema, conjunctival edema, and discharge occurred in 1 of 6 treated eyes, but aqueous flare and cells were not observed.

In 8 monkeys with unilateral glaucoma, administration to the glaucomatous eye of a single dose of 0.05%, 0.1%, and 0.2% 8-iso PGE₂ reduced (P<.01) the IOP for as long as 2, 5, and 3 hours, respectively. The maximum reduction in IOP occurred 2 hours after dosing with each of the 3 concentrations and was 4.6 ± 0.9 mm Hg (0.05%), 6.0 ± 0.8
MATERIALS AND METHODS

Fourteen female cynomolgus monkeys, each weighing 3 to 5 kg, were used in this study. Six of the animals had IOPs in the normal range. In 8 of the animals, glaucoma had been induced unilaterally by repeated argon laser (65-120 spots; power, 1.1-1.5 W; size, 50 µm; duration, 0.5 second) or diode (60-120 spots; power, 1.1-1.2 W; size, 75 µm; duration, 0.5 second) photo-coagulation of the midtrabecular meshwork for 360°.

On each day of the study, the IOP was measured with a calibrated pneumotonometer (Model 30 classic, Mentor Inc, Norwell, Mass) before drug administration (baseline), at 0.5 hour, and then hourly until 6 hours after drug administration. Five minutes before tonometry, 0.5% proparacaine hydrochloride, 1 drop, was applied topically, and ketamine hydrochloride, 1 to 5 mg/kg of body weight, was administered intramuscularly for adequate sedation. The pupil diameter was measured in normal monkeys with a millimeter ruler under standard illumination immediately before and after each IOP measurement. Slitlamp examination for the detection of aqueous humor flare and cells was performed in a dark room before drug treatment and at 1, 3, and 5 hours after treatment (Figure 3).

The magnitude and duration of the ocular hypotensive effect were enhanced with twice-a-day administration (Table). A significant correlation was found between the IOP reduction and the increase of outflow facility (r = 0.81, P < .05). The coefficient of determination (r² = 0.66) indicated that the increase in outflow facility accounted for most of the IOP reduction in these normal monkey eyes.

For 4 hours following the administration of a single dose of 0.1% 8-iso PGE₂ to the treated eyes of 6 normal monkeys, aqueous humor flow rates were unchanged (P > .10) compared with baseline values or values obtained in the contralateral vehicle-treated eyes (Table).

COMMENT

Single-dose administration of PGE₁ and PGE₂ to rabbits and PGE₂ to normotensive volunteers ultimately reduced the IOP after an initial rise. In contrast to PGE₁ and PGE₂, several PGE derivatives—RS-61565 and RS-20216—specific for the EP₃ prostanoid receptor, produced greater reductions of the IOP without an initial ocular hypertensive response and less ocular irritation. In the present study, initial ocular hypertension was not observed following single doses of 8-iso PGE₁ in normal and in glaucomatous mon-
key eyes. A dose-dependent ocular hypotensive effect was observed in the glaucomatous monkey eyes, with 0.1% 8-iso PGE$_2$ producing a greater magnitude and a longer duration of IOP reduction than the 0.05% concentration. Increasing the concentration to 0.2% did not increase the magnitude of the IOP reduction. The 0.1% 8-iso PGE$_2$ dosage produced measurements that appeared to be near the top of the dose-response curve and, with twice-a-day administration, produced a sustained reduction of IOP for 5 days in glaucomatous monkey eyes. The prostanoid-receptor profile of 8-iso PGE$_2$ has not been reported.

The effect of PGF$_{2\alpha}$ on outflow facility measured in cynomolgus monkeys has varied from increases of 25% to no increases at all.\textsuperscript{10,11} Clinical trials, however, demonstrated only small increases in tonographically measured outflow facility in patients with ocular hypertension or primary open angle glaucoma following the topical administration of PGF$_{2\alpha}$-isopropyl ester\textsuperscript{12} or PhXA34.\textsuperscript{13} Compared with PGF$_{2\alpha}$, the administration of 8-iso PGE$_2$ gave a consistent increase in tonographic outflow facility of 50% in monkeys (Table), with little effect on aqueous humor flow. Analysis of linear regression in the present study shows an apparent close relationship ($r = 0.81$, $P < .01$) between IOP reduction and increased pressure-dependent outflow facility. If several assumptions are made, eg, episcleral venous pressure is unchanged, the coefficient determination ($r^2 = 0.66$) indicates that more than two thirds of the reduction of IOP induced by 8-iso PGE$_2$ may be explained by the increase in outflow facility measured tonographically. Previous studies\textsuperscript{14-16} have demonstrated that PGF$_{2\alpha}$ congeners can enlarge the spaces between the ciliary muscle bundles, reduce their connective tissue content, and increase uveoscleral outflow, which under normal circumstances is predominantly pressure independent. This is the
The predominant ocular hypotensive mechanism of drugs response of IOP in normal monkey eyes, in contrast to the glaucoma compared with values obtained in vehicle-treated eyes on the control baseline day (2-tailed Bonferroni t test, P < .05).

In this study, a few adverse ocular effects are noted, including mild eyelid edema, conjunctival edema and discharge, mild conjunctival hyperemia, and superficial punctate keratopathy, the last observed in 1 glaucomatous monkey eye during the multiple-dose study. These findings may be related to the frequent tonometry and instillation of local anesthetic drugs or to the relatively high dose of 8-iso PGE₂. Changes in the formulation may reduce or eliminate these adverse effects if caused by the drug itself.

CONCLUSIONS

The application of 8-iso PGE₂, which is structurally different from PGF₂α and PGE₂, reduces the IOP in both normal and glaucomatous monkey eyes with few adverse effects. A high correlation exists between the reduction of IOP and the increase of tonographic outflow facility; the latter appears to account for most of the reduction in trabecular facility. Furthermore, in isolated human anterior-segment preparations that measure only outflow resistance to PGE₂,¹⁰ but not PGF₂α,¹⁷ increases facility. Based on the comparison with PGF₂α, we interpret the tonographic response to 8-iso PGE₂ to be the result of an increase in trabecular outflow facility rather than any alternative explanation.¹⁰ However, iso-prostaglandins could cause uveoscleral outflow to become more pressure dependent, and this mechanism may contribute to the measured tonographic facility.

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Aqueous Humor Dynamics Measurements With the Administration of 0.1% 8-iso ProstaglandineE₂ (8-iso PGE₂) in 6 Normal Monkeys*  

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Intraocular Pressure, mm Hg</th>
<th>Outflow Facility, µL/min/mm Hg*</th>
<th>Aqueous Humor Flow, µL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-iso PGE₂</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>13.0 ± 0.7†</td>
<td>0.83 ± 0.10†</td>
<td>1.88 ± 0.21</td>
</tr>
<tr>
<td>Baseline</td>
<td>16.3 ± 1.1</td>
<td>0.58 ± 0.03</td>
<td>1.69 ± 0.29</td>
</tr>
<tr>
<td>Vehicle‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>15.7 ± 0.5</td>
<td>0.56 ± 0.06</td>
<td>1.78 ± 0.22</td>
</tr>
<tr>
<td>Baseline</td>
<td>15.7 ± 0.6</td>
<td>0.51 ± 0.04</td>
<td>2.01 ± 0.21</td>
</tr>
</tbody>
</table>

*Data are given as means ± SEM.
†Significantly different from either baseline values or those obtained in contralateral vehicle-treated control eyes (2 tailed paired t test, P < .05).
‡Vehicle consists of 0.1% isotonic sodium chloride.

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REFERENCES


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