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-\[5Z,8\]B-11X,13E,155\]-) 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. Tonometer outflow facility and fluorophotometric flow rates of aqueous humor were measured in 6 normal monkeys and monkeys with glaucoma 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.


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 mm Hg (0.1%), and 5.8 ± 0.8 mm Hg (0.2%).
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) photocoagulation 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.

8-Isoto-PGE2 (prosta-5,13-dien-1-oic acid, 11,15-dihydroxy-9-oxo,-[5Z,8,13,15]), Cayman Chemical Co Inc, Ann Arbor, Mich) was freshly prepared by dissolving in dimethyl sulfoxide (100 g/L). This stock solution was further diluted with 0.9% sodium chloride to 0.05%, 0.1%, and 0.2% concentrations. Single-dose testing was performed in 6 normal monkeys with the 0.1% concentration and in 8 glaucomatous monkey eyes with 0.05%, 0.1%, and 0.2% concentrations. In normal monkeys, one 25-µL drop of 8-iso PGE2 was randomly applied to 1 eye, and an equal volume of isotonic sodium chloride solution (the vehicle) was applied to the contralateral control eye. In the monkeys with glaucoma, the first day was the baseline day, and one 25-µL drop of isotonic sodium chloride was administered to the glaucomatous eye at 9:30 AM. On the second day, 25 µL of 8-iso PGE2 was applied to the glaucomatous eye at 9:30 AM. Following 1 baseline day (neither vehicle nor drug was administered) and 1 vehicle-treated day (vehicle to the glaucomatous eye at 9:30 AM and 3:30 PM), a multiple-dose study was carried out in 8 monkeys with unilateral glaucoma, with 0.1% 8-iso PGE2 applied to the glaucomatous eye twice a day (at 9:30 AM and 3:30 PM) for 5 consecutive days.

Outflow facility was measured with an electronic indentation tonograph (EDT-103, Alcon Laboratories, Inc, Ft Worth, Tex) 4 hours before dosing and was remeasured 2 hours after unilateral dosing with one 25-µL drop of 0.1% 8-iso PGE2 in 6 normal monkeys. Aqueous humor flow was measured with a scanning computerized fluorophotometer (Coherent Fluorotron, Coherent Corp, Palo Alto, Calif) in 6 normal monkeys. (Breakdown of the blood-aqueous barrier in glaucomatous monkey eyes makes them poor models to use for aqueous flow measurements.) Iontophoresis was performed in the central corneas of both eyes of each monkey for 7 minutes using 10% fluorescein in 2% agar gel at 4 PM on the day before aqueous flow measurements. Baseline aqueous humor flow rates were measured hourly for 4 hours beginning at 9:30 AM. The following day, one 25-µL drop of 0.1% 8-iso PGE2 was applied to 1 eye of each monkey, and the same volume of vehicle was instilled in the contralateral eye at 8:30 AM. Flow rates were measured at the same times as on the baseline day beginning 1 hour after drug administration. The washout period between each test on the same animal was at least 1 week.

The 2-tailed paired t test was used for statistical analysis before and after single-dose treatment, and the Bonferroni t test was used for the analysis of the multiple-dose study. The Pearson product moment correlation coefficient was used to analyze the relationship between IOP and outflow facility. All experimental studies complied with the Association for Research in Vision and Ophthalmology Resolution on the Use of Animals in Research and were approved by the Mount Sinai School of Medicine, New York, NY, Institutional Animal Care and Utilization Committee.

Data are given as mean ± SEM.
key eyes. A dose-dependent ocular hypotensive effect was observed in the glaucomatous monkey eyes, with 0.1% 8-iso PGE₂ 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 PGE₂ 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 PGE₂ has not been reported.

The effect of PGF₂α on outflow facility measured in cynomolgus monkeys has varied from increases of 25% to no increases at all. 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 PGF₂α-isopropyl ester or PhXA34. Compared with PGF₂α, the administration of 8-iso PGE₂ 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 (r² = 0.66) between IOP reduction and increased pressure-dependent outflow facility. If several assumptions are made, e.g., episcleral venous pressure is unchanged, the coefficient determination (r² = 0.66) indicates that more than two thirds of the reduction of IOP induced by 8-iso PGE₂ may be explained by the increase in outflow facility measured tonographically. Previous studies have demonstrated that PGF₂α 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 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 the IOP and the increase of tonographic outflow facility; the latter appears to account for most of the reduction of IOP in normal eyes, in contrast to the predominant ocular hypotensive mechanism of drugs related to PGF₂α, such as latanoprost. These findings have possible clinical relevance because they show that prostaglandins with unusual stereochemical or geometric configurations can affect aqueous humor dynamics by different mechanisms than those with the normal stereochemistry and geometric configuration that are in current clinical use.

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 the IOP and the increase of tonographic outflow facility; the latter appears to account for most of the reduction of IOP in normal eyes, in contrast to the predominant ocular hypotensive mechanism of drugs related to PGF₂α, such as latanoprost. These findings have possible clinical relevance because they show that prostaglandins with unusual stereochemical or geometric configurations can affect aqueous humor dynamics by different mechanisms than those with the normal stereochemistry and geometric configuration that are in current clinical use.