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The Effect of Prostaglandin F₂α on Intraocular Pressure in Normotensive Human Subjects

Ping-Yu Lee, Hui Shao, Liang Xu, and Chan-Kuei Qu

Hypotensive and other ocular effects were studied for 24 hr after topical application of prostaglandin F₂α as the tromethamine salt (PGF₂α) in 45 normotensive human subjects. After baseline intraocular pressure (IOP) measurements, 62.5 ng, 125 μg, and 250 μg of PGF₂α dissolved in 50 μl of saline was applied to one eye of 15 subjects for each dose tested. Contralateral control eyes received 50 μl of saline. As compared with the IOP of the contralateral control eyes, topical application of 62.5 ng PGF₂α caused a significant IOP reduction at 1–12 hr, with a maximal IOP reduction of 2.2 mm Hg at 2 hr. Treatment with 125 μg of PGF₂α lowered IOP significantly at 1–21 hr, with a maximal reduction of 3.1 mm Hg at 9 hr. Administration of 250 μg PGF₂α produced a significant reduction of IOP, which lasted for at least 24 hr. A maximal IOP reduction of 2.9 mm Hg occurred at 7 hr. Pupillary diameter was not altered. Aqueous flare and anterior chamber cellular response were not seen in any of the eyes of the subjects at any time after topical application of 62.5–250 μg PGF₂α. The drug caused side effects consisting of reddened skin of lower lid, ocular irritation, conjunctival hyperemia and headache.

Single-dose studies have shown that a highly significant and prolonged reduction of intraocular pressure (IOP) occurred following topical application of several prostaglandins (PGs) in normotensive rabbit, cat, and monkey eyes with no adverse effect, or with only minimal inflammation. Also, a single dose of topically applied PGF₂α significantly reduced IOP in glaucomatous eyes of monkeys.

Multiple-dose studies have demonstrated that topical application of PGE₂ once or twice daily in cats produced a maintained reduction of IOP for at least 9 months. Topical application of PGF₂α twice daily in normal monkeys showed no evidence of tolerance or tachyphylaxis developing to the hypotensive response for several days to weeks. Twice daily dosing with PGF₂α for 2 weeks reduced IOP as much as 13 mm Hg in the glaucomatous monkey eyes. There was no evidence of tolerance or tachyphylaxis during the course of treatment.

A single topical application of 200 μg of PGF₂α tromethamine salt produced a significant reduction of IOP for at least 24 hr in 18 nonglaucomatous human subjects. Topical application of PGF₂α-propylster 0.5 μg at 8 AM and 8 PM for 1 day produced significant reduction of IOP in 12 patients with chronic open angle or exfoliative glaucoma.

The purpose of the current study was to investigate the hypotensive and other ocular effects of PGF₂α on normotensive human subjects.

Materials and Methods

Forty-five normotensive human subjects, 36 females and nine males, were studied. Their ages ranged from 20 to 59 years (average age of 37). The subjects’ informed consent was obtained. An ocular examination was performed to confirm that no ocular disease was present and that the two eyes had similar IOPs (within 3 mm Hg) which were less than or equal to 21 mm Hg.

IOP was measured with a calibrated pneumatonometer (Model 30R; Digilab, Inc., Cambridge, MA) following topical application of one drop of oxybuprocaine hydrochloride 0.4% (Dispersa Ltd., Hettlingen, Switzerland). Horizontal pupil diameter was measured in 0.5 mm increments with a millimeter ruler under standard room illumination. The aqueous humor flare and cellular response in the anterior chamber were assessed by slit-lamp examination.

Each milliliter of the stock solution (Upjohn Co., Kalamazoo, MI) contained PGF₂α tromethamine salt equivalent to 5 mg PGF₂α, and benzyl alcohol, 9.45 mg, added as a preservative. The stock solution was diluted with normal saline to yield concentration...
containing 62.5 μg, 125 μg or 250 μg PGF2α in 50 μl. For all subjects, the study began between 8:30 AM and 9:30 AM. After baseline measurements of IOP, pupil diameter, and slit-lamp examination, 50 μl of the PGF2α solution was applied to one eye of 15 subjects for each dose tested. Contralateral control eyes received 50 μl normal saline. Repeat measurements were made at 0.5, 1, 2, 3, 5, 7, 9, 12, 15, 21 and 24 hr after the drug administration.

Statistical significance of results was determined by use of two-tailed, paired t-test. Discrimination of levels of probability were made at \( P > 0.05 \), \( P < 0.05 \), \( P < 0.01 \) and \( P < 0.001 \).

### Results

Topical administration of 62.5 μg, 125 μg or 250 μg of PGF2α to one eye of normotensive human subjects resulted in reduction of IOP (Table 1). The difference in IOP between the treated eyes and the contralateral control eyes is shown in Figure 1.

As compared with the IOP of the contralateral control eyes, topical application of 62.5 μg of PGF2α produced a significant reduction of IOP at 1 hr (\( P < 0.05 \)), 2 hr (\( P < 0.01 \)), 3-7 hr (\( P < 0.001 \)), and 9-12 hr (\( P < 0.05 \)) after the drug administration, with a maximal IOP reduction of 2.2 ± 0.6 mm Hg (mean ± SEM) at 2 hr. As compared with the baseline values, the mean IOP was reduced significantly at 2 hr (\( P < 0.001 \)), 3 hr (\( P < 0.01 \)), and 5-15 hr (\( P < 0.001 \)), with a maximal IOP reduction of 3.4 ± 0.6 mm Hg at 7 hr.

As compared with contralateral control values, treatment with 125 μg of PGF2α lowered IOP significantly at 1 hr (\( P < 0.05 \)), 2 hr (\( P < 0.01 \)), 3-12 hr (\( P < 0.001 \)), 15 hr (\( P < 0.01 \)), and 21 hr (\( P < 0.05 \)) in the treated eyes, with a maximal IOP reduction of 3.1 ± 0.4 mm Hg at 9 hr. As compared with the baseline values, a significant reduction in IOP was present at 1-24 hr (\( P < 0.001 \)), with a maximal reduction of 5.1 ± 0.5 mm Hg at 12 hr.

As compared with the contralateral control eyes, administration of 250 μg PGF2α resulted in a significant reduction of IOP in treated eyes at 1 hr (\( P < 0.01 \)), 2 hr (\( P < 0.001 \)), 3 hr (\( P < 0.01 \)), 5-12 hr (\( P < 0.001 \)), 15 hr (\( P < 0.05 \)), and 24 hr (\( P < 0.001 \)), with a maximal IOP reduction of 2.9 ± 0.7 mm Hg at 7 hr. As compared with the baseline values, the IOP was reduced significantly at 1-24 hr (\( P < 0.001 \)), with a maximal reduction of 5.4 ± 0.7 mm Hg at 12 hr.

### Table 1. Effects of prostaglandin F2α on intraocular pressure

<table>
<thead>
<tr>
<th>Dose of PGF2α (μg)</th>
<th>0.5 hr</th>
<th>1 hr</th>
<th>2 hr</th>
<th>3 hr</th>
<th>5 hr</th>
<th>7 hr</th>
<th>9 hr</th>
<th>12 hr</th>
<th>24 hr</th>
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<tbody>
<tr>
<td>Control</td>
<td>17.2 ± 0.4</td>
<td>16.7 ± 0.5</td>
<td>16.7 ± 0.5</td>
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<tr>
<td>PGF2α (62.5 μg)</td>
<td>16.9 ± 0.6</td>
<td>16.7 ± 0.5</td>
<td>16.7 ± 0.5</td>
<td>16.7 ± 0.5</td>
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</tr>
<tr>
<td>PGF2α (125 μg)</td>
<td>15.3 ± 0.4</td>
<td>15.2 ± 0.5</td>
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<tr>
<td>PGF2α (250 μg)</td>
<td>14.5 ± 0.7</td>
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Pupillary diameter was not altered significantly. Neither aqueous humor flare nor anterior chamber cellular response were seen in any of the eyes of the subjects at any time.

All doses of PGF2α tested produced ocular irritation and a foreign body sensation immediately after
Fig. 1. Differences of IOP between the PG-treated eyes and the contralateral control eyes of 15 subjects for each dose tested (A: 62.5 μg/eye; B: 125 μg/eye; C: 250 μg/eye). Points represent the mean differences and the limits ± 1 SEM.

the drug administration that lasted for 0.5–1 hr in treated eyes in all subjects. Immediately after topical application of PGF₂α, a marked conjunctival hyperemia was observed in the treated eyes in all subjects. The hyperemia persisted for 9–12 hr after application of 62.5 μg or 125 μg PGF₂α and for 12–24 hr after application of 250 μg PGF₂α. Erythema of the skin of the lower lid was noted in two of the 15 treated eyes following 125 μg or 250 μg PGF₂α instillation. This effect was reduced after 10 hr in the 125 μg treatment group and after 12 hr in the 250 μg treatment group. Moreover, 50% of the subjects in 125 μg or 250 μg treatment group had a slight headache, which generally resolved after 2–3 hr.

Discussion

The results presented here indicate that topical administration of 62.5 μg, 125 μg or 250 μg PGF₂α to one eye of normotensive human subjects causes a significant IOP reduction. Topical use of this drug group did not significantly affect pupillary diameter, and did not cause aqueous humor flare or anterior chamber cellular response. These findings are similar to previous observations.¹²

Giuffré¹² has observed that topical application of 200 μg PGF₂α tromethamine salt produced a significant reduction of IOP of as much as 4 mm Hg, peaking at 7–10 hr, when compared with either contralateral control eyes or baseline values in 18 normotensive human subjects. A significant reduction of IOP persisted as long as 24 hr after a single application. No miosis was noted. There was no evidence of breakdown of the blood-aqueous barrier as determined by slit-lamp examination for aqueous flare.

The mechanism of the ocular hypotensive effect of the PGs in general is not known. Suggestions include: (1) increased outflow facility¹²; (2) reduced aqueous production¹⁰; and (3) increased uveoscleral outflow.¹⁴–¹⁶ Further studies are necessary with PGs in the hope of clearly defining their mechanism of action.

In our studies, there are unfavorable side effects of ocular irritation, conjunctival hyperemia and headache. These findings are consistent with previous observations.¹²,¹³

PGs reduce IOP in single and/or multiple dose testing without evidence of tolerance or tachyphylaxis in experimental animals. Significant IOP reductions have been observed in PG-treated human eyes without the induction of flare, cellular response or miosis. They seem to show potential as new ocular hypotensive agents. The task remains, however, to conduct tests with various PG analogues to determine which is most effective with the least local and systemic side effects.

Key words: prostaglandin F₂α, intraocular pressure, ocular hypotension

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References