The Effect of Prostaglandin F\textsubscript{2α} 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 \( \text{F}_2\alpha \), as the tromethamine salt (PGF\(_{2\alpha}\)), in 45 normotensive human subjects. After baseline intraocular pressure (IOP) measurements, 62.5 \( \mu \)g, 125 \( \mu \)g and 250 \( \mu \)g of PGF\(_{2\alpha}\) dissolved in 50 \( \mu \)l of saline was applied to one eye of 15 subjects for each dose tested. Contralateral control eyes received 50 \( \mu \)l of saline. As compared with the IOP of the contralateral control eyes, topical application of 62.5 \( \mu \)g PGF\(_{2\alpha}\) 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 \( \mu \)g of PGF\(_{2\alpha}\) lowered IOP significantly at 1–21 hr, with a maximal reduction of 3.1 mm Hg at 9 hr. Administration of 250 \( \mu \)g PGF\(_{2\alpha}\) 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 \( \mu \)g PGF\(_{2\alpha}\). 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,\textsuperscript{1–3} cat,\textsuperscript{2,4,5} and monkey\textsuperscript{2,4,6} eyes with no adverse effect, or with only minimal inflammation. Also, a single dose of topically applied PGF\(_{2\alpha}\), significantly reduced IOP in glaucomatous eyes of monkeys.\textsuperscript{6,7}

Multiple-dose studies have demonstrated that topical application of PGE\(_2\) once or twice daily in cats produced a maintained reduction of IOP for at least 9 months.\textsuperscript{8} Topical application of PGF\(_{2\alpha}\) twice daily in normal monkeys showed no evidence of tolerance or tachyphylaxis developing to the hypotensive response for several days to weeks.\textsuperscript{8–10} Twice daily dosing with PGF\(_{2\alpha}\) 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.\textsuperscript{11}

A single topical application of 200 \( \mu \)g of PGF\(_{2\alpha}\) tromethamine salt produced a significant reduction of IOP for at least 24 hr in 18 nonglaucomatous human subjects.\textsuperscript{12} Topical application of PGF\(_{2\alpha}\)-iso-propylester 0.5 \( \mu \)g at 8 AM and 8 PM for 1 day produced significant reduction of IOP in 12 patients with chronic open angle or exfoliative glaucoma.\textsuperscript{13}

The purpose of the current study was to investigate the hypotensive and other ocular effects of PGF\(_{2\alpha}\) 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\textsuperscript{7} pneumotonometer (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 PGF\(_{2\alpha}\) tromethamine salt equivalent to 5 mg PGF\(_{2\alpha}\), 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 $2.2 \pm 0.6$ 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 $3.4 \pm 0.6$ 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 $3.1 \pm 0.4$ mm Hg at 9 hr. As compared with the baseline values, a significant reduction in IOP was present at 1–15 hr and 24 hr ($P < 0.001$), with a maximal reduction of $5.1 \pm 0.5$ 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 $2.9 \pm 0.7$ 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 $5.4 \pm 0.7$ mm Hg at 12 hr.

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

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Time after administration. Difference between PG-treated and control eyes was significant by the two-tailed, paired t-test: $*P < 0.05$, $**P < 0.01$, $***P < 0.001$. **
the drug administration that lasted for 0.5–1 hr in treated eyes in all subjects. Immediately after topical application of PGF\(_2\alpha\), 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 \(\mu\)g or 125 \(\mu\)g PGF\(_2\alpha\) and for 12–24 hr after application of 250 \(\mu\)g PGF\(_2\alpha\). Erythema of the skin of the lower lid was noted in two of the 15 treated eyes following 125 \(\mu\)g or 250 \(\mu\)g PGF\(_2\alpha\) instillation. This effect was reduced after 10 hr in the 125 \(\mu\)g treatment group and after 12 hr in the 250 \(\mu\)g treatment group. Moreover, 50% of the subjects in 125 \(\mu\)g or 250 \(\mu\)g 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 \(\mu\)g, 125 \(\mu\)g or 250 \(\mu\)g PGF\(_2\alpha\) 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.\(^2\)

Giuffrè\(^2\) has observed that topical application of 200 \(\mu\)g PGF\(_2\alpha\) 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 facility\(^1,2\); (2) reduced aqueous production\(^10\); 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.\(^1,2\)

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 F\(_2\alpha\), intraocular pressure, ocular hypotension

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**References**