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Reduction of intraocular pressure in normal and glaucomatous primate *(Aotus trivirgatus)* eyes by topically applied prostaglandin $F_{2\alpha}$

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ABSTRACT

Topical application of a single dose of 1.0 mg prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) onto the cornea of five trained owl monkeys (Aotus trivirgatus) caused a prolonged and highly significant ocular hypotony. The intraocular pressure (IOP) of the treated eye was 4.7 ± 0.9 mm Hg below that of the control eye 18 to 24 hr after $PGF_{2\alpha}$ application and remained significantly reduced for over 72 hr. Miosis, aqueous flare, and accumulation of cells in the anterior chamber were minimal in extent. The hypotensive effect of $PGF_{2\alpha}$ was even more pronounced when applied to a glaucomatous owl monkey eye with angle recession, which had IOPs consistently in the 45 to 55 mm Hg range (mean: 47.2 ± 0.7) as measured periodically over a one-year period. The application of a single dose of 1.0 mg of $PGF_{2\alpha}$ to this hypertensive eye reduced IOP by over 25 mm Hg within 4 hr, with a relative hypotony lasting for at least 6 days. These results show that topical application of certain PGs to normotensive or hypertensive primate eyes can cause a long lasting and highly significant decrease in IOP, and suggest that prostaglandins or their analogues may aid in the therapeutic control of ocular hypertension and glaucoma.

INTRODUCTION

Earlier studies on the ocular effects of prostaglandins (PGs) describing changes in IOP, pupillary diameter, and protein concentration in the aqueous humor were mostly limited to observations during the first few hours after administration of relatively high doses of these autacoids. On the basis of such studies, it was concluded that PGs cause a severe ocular inflammatory response characterized by marked ocular hypertension, pupillary miosis, and a breakdown of the blood-aqueous barrier (1). More recently, it was shown that low doses of $PGF_{2\alpha}$ applied topically to rabbit eyes cause a highly significant and long lasting reduction in IOP which is associated with increased outflow facility, but is not mediated by the sympathetic nervous system or by endogenous PG synthesis (2).

The few reported studies on ocular effects of PGs in monkeys or humans indicate that the primate eye is considerably less sensitive than the rabbit eye to the inflammatory effects of PGs (3,4,5,6). However, no studies have been reported on primate eyes which follow IOP changes past the first 90 min after topical application of PGs.

In the present experiments, the floating tip pneumatic tonometer was used on trained, conscious owl monkeys so that changes in IOP could be measured periodically for several days after topical application of $PGF_{2\alpha}$. This study included one owl monkey which had a long-standing unilateral angle recession glaucoma of unknown origin.

MATERIALS AND METHODS

Five normal owl monkeys (Aotus trivirgatus; 3 males and 2 females; 0.8 to 1.0 kg) and one female with unilateral angle recession glaucoma were conditioned, as previously described (7), to accept handling, restraint, and tonometry without anesthesia. The IOP of both eyes was measured over a one-year period at random intervals, but at least once each month. One drop of 0.5% proparacaine hydrochloride (Alcaine; Alcon Corp., Fort Worth, TX) was applied to the eye before IOP was measured with a floating tip pneumatic tonometer probe (8) attached to a pressure transducer and a recorder as described before (7). Each animal was placed in the supine position on the lap of the investigator and 2 or 3 IOP measurements, each several seconds in duration, were taken. The best steady-state segments of the IOP tracings were read and averaged. Pupillary diameter was measured in normal room light with a pupil gauge. Anterior chamber flare and cellular invasion were determined by slit lamp examination and rated as previously described (9).

The tromethamine salt of $PGF_{2\alpha}$ (a gift from Dr. John E. Pike, The Upjohn Co., Kalamazoo, Mich.) was dissolved in physiological saline to yield $PGF_{2\alpha}$ concentrations of 20, 40, 80 or 200 mg/ml. In each experiment 5 µl of one of these solutions was applied to one eye of each monkey. The eyes were rinsed 3 to 5 min later with 2 to 4 ml of saline. An equal volume (5 µl) of saline was similarly applied to the contralateral control eyes followed by rinsing. Measurements of IOP, pupillary diameter, and slit lamp evaluation of aqueous flare and cellular content of the anterior chamber were made at various intervals after $PGF_{2\alpha}$ application.

RESULTS

Studies on normal owl monkey eyes

Topical application of 0.2 mg of $PGF_{2\alpha}$ to one eye (left eye in 2 and right eye in 3 animals) of the 5 normal owl monkeys did not result in significant effects on the IOP as compared to the baseline IOP of the treated eye or the simultaneously measured IOP in the contralateral eye (Table 1). However, topical application of 1 mg of $PGF_{2\alpha}$ to the left eye of these animals 4 to 14 days after the first trial resulted in a prolonged hypotony in the treated eye compared with the contralateral eye (Fig. 1). In 3 of the 5 eyes this hypotony was preceded by a 2-3 mm Hg rise in IOP occurring 15 min after treatment and showing borderline significance compared with the contralateral eye (Table 1). A prolonged hypotony was also observed when the same dose of $PGF_{2\alpha}$ was applied 6 days later to the contralateral (right) eyes of these monkeys, or when it was applied 18 days later to the originally treated eyes (Table 1). Although the extent of ocular hypotension in the treated eye was about the same after each application of 1.0 mg of $PGF_{2\alpha}$, the significance of the IOP differences between treated and contralateral eyes was reduced on subsequent PG application because of an apparent contralateral hypotensive effect. These IOP effects on the untreated contralateral eyes were not due to diurnal variations since tonometry done over a 24-hr period on the eyes of these same animals after bilateral saline-treatment or after unilateral treatment with a low dose of (0.2 mg) $PGF_{2\alpha}$ did not show significant lowering of IOP (Table 1).

TABLE 1. The effects of topically applied $PGF_{2\alpha}$ on the IOP of five normal owl monkeys

$PGF_{2\alpha}$ Treatment (dose/eye) Date	Time (in hrs)*	IOP (mm Hg; mean ± SEM) A Treated Eye	B Control Eye	p** A vs B
0.2 mg	-0.25	19.4 ± 0.2	19.2 ± 0.4	NS
O.D. or	+0.25	20.8 ± 0.6	20.0 ± 0.8	NS
O.S.	+ 4	17.8 ± 1.2	19.2 ± 1.2	NS
8/11/78	+ 8	19.0 ± 2.0	21.0 ± 2.0	NS
or 8/21/78	+24	18.4 ± 1.2	19.0 ± 1.1	NS
1.0 mg	-0.25	18.8 ± 0.3	19.0 ± 0.4	NS
O.S.	+0.25	21.8 ± 1.0	20.4 ± 1.6	<0.1
8/25/78	+ 4	15.4 ± 0.7	17.4 ± 0.8	<0.01
	+ 8	12.0 ± 1.0	16.2 ± 1.2	<0.001
	+12	11.6 ± 0.7	15.8 ± 0.8	<0.001
	+24	14.2 ± 0.4	19.0 ± 0.6	<0.001
1.0 mg	-0.25	19.0 ± 0.8	19.0 ± 0.8	NS
O.D.	+0.25	21.2 ± 0.6	19.4 ± 0.8	<0.05
8/31/78	+ 4	17.6 ± 1.1	17.6 ± 1.3	NS
	+ 8	13.2 ± 1.0	16.0 ± 1.7	<0.05
	+12	11.6 ± 0.8	14.6 ± 1.2	<0.05
	+24	14.2 ± 1.4	16.8 ± 1.0	<0.05
1.0 mg	-0.25	16.6 ± 0.8	16.4 ± 0.7	NS
O.S.	+0.5	19.6 ± 1.5	18.8 ± 1.2	NS
9/12/78	+ 4	14.6 ± 1.7	14.6 ± 1.8	NS
	+12	12.6 ± 0.9	16.0 ± 1.5	<0.05
	+24	18.6 ± 1.7	21.4 ± 1.8	NS
		O.D.	O.S.	
None	-0.25	19.8 ± 0.4	19.6 ± 0.6	NS
(Saline)	+0.25	21.2 ± 0.5	20.8 ± 0.6	NS
O.U.	+ 4	20.6 ± 0.9	20.4 ± 0.9	NS
9/26/78	+ 8	21.4 ± 1.2	21.6 ± 1.3	NS
	+12	19.8 ± 0.9	19.6 ± 1.2	NS
	+24	20.0 ± 0.8	20.2 ± 0.9	NS

*time in hrs before (negative value) or after the topical application of $PGF_{2\alpha}$ to one eye and an equal volume (5 µl) of saline to the contralateral eye of each animal. In the last experiment: hrs before or after application of 5 µl saline to both eyes (O.U.).

**2-tailed paired Student's t-test; NS: p>0.1.

One half hour after topical application of 1.0 mg $PGF_{2\alpha}$, there was an average of 2.0 ± 0.3 mm pupillary miosis compared to the contralateral control eyes. A gradual return to normal pupil size (4.8 ± 0.2 mm) occurred over the next 18 hr. Slight aqueous flare was present in 4 of 5 eyes between 2 and 12 hr after the topical application

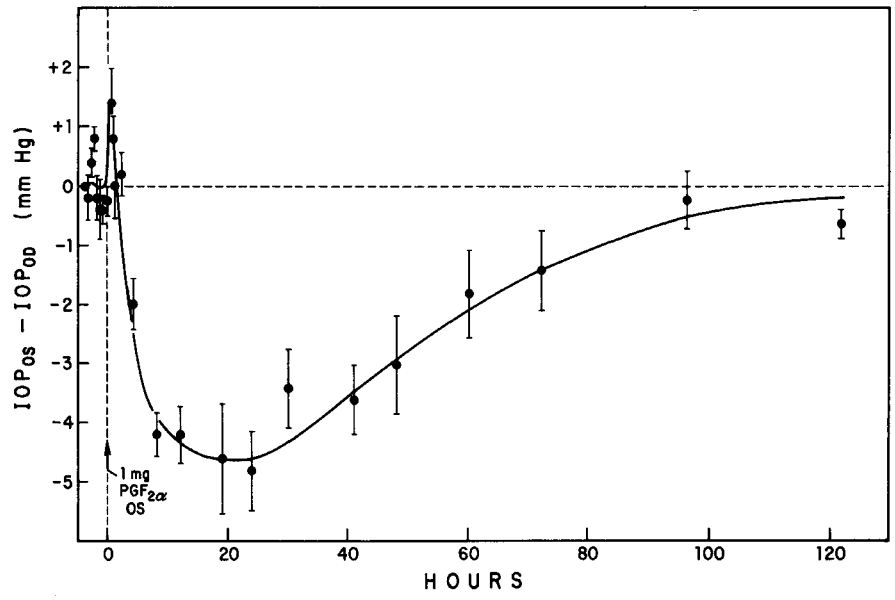

Figure 1. The effects of topically applied $PGF_{2\alpha}$ (1.0 mg/eye) on the IOP of normal owl monkey eyes relative to the IOP of the contralateral (saline treated) control eye. The points represent the mean of the differences in IOP (treated-control eye) obtained on five animals and the limits represent ± 1 SEM.

of 1.0 mg of $PGF_{2\alpha}$. At 48 hr, a few cells were observed in 3 of the 5 treated, but in none of the control eyes. There was no apparent correlation between IOP reduction and the presence of flare and cells in the anterior chamber, i.e. the ocular hypotension was not associated with a notable inflammatory response.

Studies on a glaucomatous owl monkey eye

When purchased, one female monkey had eyes exhibiting a marked anisocoria with the right pupil being a consistent 2 mm larger than the left. Gonioscopic examination of the right eye revealed angle recession. Ophthalmoscopic examination by a practicing ophthalmologist (Dr. B. D. Srinivasan) revealed asymmetric cup-to-disc ratios with deep excavation of the cup and temporal disc pallor in the right eye. The cornea of this eye showed diffuse stromal haze and moderate edema with microcystic changes, but there was no evidence of endothelial cell loss, corneal scars or recent injury to the eye. Ultrasonic measurements by Dr. Jackson Coleman's laboratory showed anterior chamber depths of 4.4 and 3.7 mm and axial lengths of 14.6 and 12.7 mm for the right and left eyes, respectively. Repeated examination over a one-year period prior to the time $PGF_{2\alpha}$ was applied showed that the pupillary diameter of the right eye (9 mm) was consistently larger than that of the left eye (7 mm), but both pupils constricted to 1 mm 20 min after the topical application of 0.5% pilocarpine. The mean of 46 IOP measurements taken over a period of one year was 47.2 ± 0.7 and 24.5 ± 0.6 mm Hg for the right and left eyes respectively. Eleven months before this study on the effects of $PGF_{2\alpha}$, topical application of 1% pilocarpine reduced the IOP by 4 mm Hg in the left eye, but raised the IOP of the right eye by 16 mm Hg. Oxotremorine (0.05%) also increased the IOP of the right eye.

Within 20 min after application of 1.0 mg of $PGF_{2\alpha}$ to the right eye of this owl monkey, IOP dropped from an average pretreatment value of 50 mm Hg to 32 mm Hg, followed by a more gradual decline during the next 12 hr, ultimately reaching a value similar to that of the control eye and as low as 14 mm Hg (Fig. 2). The IOP of the two eyes then remained similar for about 3 days, followed by a gradual return in the right eye to pretreatment IOP levels of 50 mm Hg. During this period of normo-

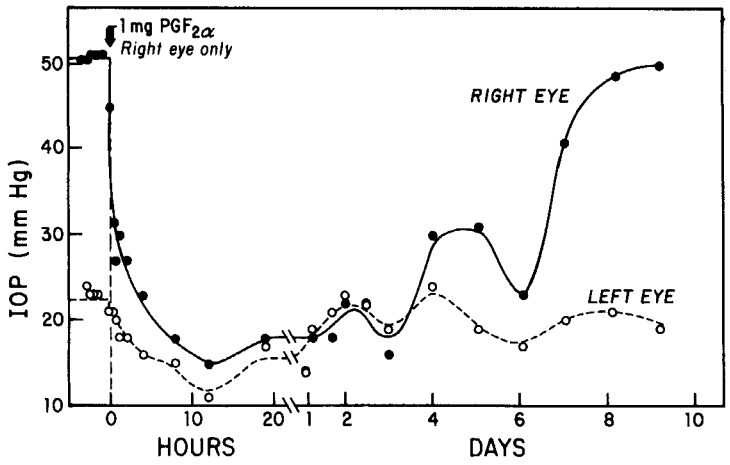

Figure 2. Reduction of IOP in a glaucomatous owl monkey eye following topical application of 1.0 mg of $PGF_{2\alpha}$.

tension, there was marked clearing of the corneal haze of the right eye, but this haze reappeared as the IOP rose to its baseline values in the 40-50 mm Hg range. However, for several weeks thereafter, the IOP of this eye appeared to be much more labile than it was before the $PGF_{2\alpha}$ application.

DISCUSSION

The present results clearly show that topically applied $PGF_{2\alpha}$ can cause a prolonged and highly significant IOP reduction in normal and glaucomatous owl monkey eyes. A dose of 1.0 mg $PGF_{2\alpha}$ in the owl monkey eye produces an IOP reduction comparable in extent to that caused by 5 µg $PGF_{2\alpha}$ in the rabbit eye (2). The need for a higher dose was anticipated, since it was shown that primates are less sensitive than rabbits to the ocular effects of PGs (3). However, the duration of IOP reduction was much longer in the owl monkeys than was previously observed in rabbits (2). This suggests that there is an inherent difference between these two species with respect to the mechanism of action and/or bioavailability of PGs. This conclusion is supported by the observation that although increasing the dose of $PGF_{2\alpha}$ increased the duration of hypotony in rabbits, this hypotony could not be extended beyond 20 hr in that species without causing a breakdown of the blood-aqueous barrier and inducing a pronounced initial increase in IOP (2).

It should be noted that the long term reduction of IOP caused by twice daily topical epinephrine application to rabbit eyes was shown to be blocked by indomethacin pretreatment (10). This suggests that the hypotony produced by epinephrine may be dependent upon endogenous synthesis of cyclooxygenase products and, in fact, the hypotony may be mediated, at least in part, by PGs.

There is accumulating evidence that the rabbit eye is singularly atypical among the eyes of vertebrates, especially with respect to some aspects of the prostaglandin system (11,12). Thus, much of the previous work on the ocular effects of PGs will have to be repeated on other species, including primates, before their applicability to the human eye can be evaluated. While there may be species variation even among primates, preliminary experiments in our laboratory (13) indicate that, like in the owl monkey, topically applied $PGF_{2\alpha}$ also has hypotensive effects on eyes of rhesus monkeys. Furthermore, it should be noted that $PGF_{2\alpha}$ was found to reduce IOP when administered by intrauterine or intravenous injection to pregnant women to induce abortions (6). These considerations suggest that topically applied PGs, or their analogues, may provide a more direct approach to the therapy of glaucoma than adrenergic agents and

related drugs.

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