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Prostaglandin $F_{2\alpha}$-isopropylester eye drops: effect on intraocular pressure in open-angle glaucoma

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SUMMARY In 30 patients with previously untreated open-angle glaucoma an intraocular pressure (IOP) curve was taken before and during treatment with $PGF_{2\alpha}$-isopropylester ($PGF_{2\alpha}$-IE) eye drops in one eye. Compared with the pretreatment IOP, the $PGF_{2\alpha}$-IE induced a slowly increasing reduction in IOP. Just before the first dose the IOP was 31·4 (SEM 1·6) mm Hg. When corrected for the fall in pressure observed in the fellow eye the largest reduction, 5·8 (SEM 0·7) mm Hg ($p<0·001$), was obtained 24 hours later, that is, 12 hours after the second dose. In a subgroup of 10 patients the treatment was continued for one week. In this group the final pretreatment IOP was 25·9 (SEM 1·3) mm Hg. The reduction 24 hours later was 4·5 (SEM 0·6) mm Hg ($p<0·001$). The effect was maintained and even slightly increased during the week, and on the seventh day of treatment the IOP reduction ranged between 4·8 and 7·6 mm Hg compared with the pretreatment IOP. No serious subjective or objective side effects were observed.

During the last decade the effect of prostaglandin eye drops on intraocular pressure (IOP) has been the subject of many studies. In low doses they are potent ocular hypotensives in rabbits, cats, and monkeys.[1–6] The drug most thoroughly tested in primates is prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). Its pressure lowering effect seems to be due to a different mechanism from that of conventional glaucoma drugs. Thus, at least in cats and primates, changes neither in outflow facility[4 6 7] nor in aqueous humour production[4–6 8] large enough to explain the effect on IOP have been found. Studies in monkeys indicate that increased uveoscleral outflow may be the major reason for the reduced IOP.[9–11]

In studies on the human eye 62·5–250 μg of the trometamol salt of $PGF_{2\alpha}$ reduces IOP 2–4 mm Hg in normotensive eyes, but with unacceptable side effects.[12–13] The lipid solubility of the trometamol salt is low, and esterification of $PGF_{2\alpha}$ markedly increases the lipid solubility.[14] Thus an ester such as $PGF_{2\alpha}$-isopropylester ($PGF_{2\alpha}$-IE) penetrates the cornea much easier than the parent drug and becomes de-esterified during its passage through the cornea.[15] As a consequence 0·5–2·0 μg $PGF_{2\alpha}$-IE is enough to reduce IOP in man.[16] This effect is not due to reduced aqueous humour flow,[16–17] and an effect on outflow facility large enough to explain the effect on IOP was not found in normal eyes.[16] Thus an increased uveoscleral outflow possibly takes place also in the human eye.

Little is known about uveoscleral outflow in humans. In monkeys it is thought to be responsible for 30–45% of the total outflow,[18] but in humans it may be only about 10%.[19] Furthermore, it is not clear to what extent results obtained in young healthy volunteers are valid also for glaucomatous eyes of elderly people. Thus the purpose of the present study is to determine whether the effect of $PGF_{2\alpha}$-IE on IOP in normal eyes can be verified also in eyes with previously untreated open-angle glaucoma. Some of the results have been briefly reported previously.[20]

Subjects and methods

DESIGN

The study was designed as an unmasked, open-label study of the effect on IOP of $PGF_{2\alpha}$-IE. The drug produces some foreign body sensation and conjunc-

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tival hyperaemia even in low doses, and a reliable masking is not possible. Determination of IOP, however, was made in a masked fashion (see below). Thirty patients were selected for treatment during one day (two doses), with the possibility of extending the treatment period to one week in 10 patients if the IOP was adequately controlled during the first day of treatment. Two centres were involved in the study. The study protocol was reviewed and approved by the National Board of Health and Welfare and by the Medical Faculty, University of Umeå.

PATIENT SELECTION

Only patients with previously untreated open angle glaucoma were included in the study. The diagnosis was based on an IOP of more than 21 mm Hg on at least three of five measurements during one day, open angle by gonioscopy, glaucomatous excavation of the optic nerve, and/or glaucomatous visual field defect. Only one eye in each patient was included in the study. In seven patients with suspected bilateral glaucoma the eye with the highest IOP was chosen. The other eye was not treated with any drug during the study. Patients with severe active or chronic systemic disease, a previous history of angle closure or secondary glaucoma, or any concomitant ocular disease were excluded. Eleven men and 19 women between 57 and 79 years of age were included. The diagnosis was glaucoma capsulare in 20 eyes and glaucoma simplex in 10 eyes.

EXAMINATION SCHEDULE

Day 0. A routine ocular examination was performed, including evaluation of the optic disc, the chamber angle, and the visual field (automatic perimetry, Competer). Repeated IOP measurements were made to confirm the diagnosis. The IOP was determined with a Goldmann tonometer, the right eye first. Five consecutive readings were done in each eye with the scale of the tonometer masked to the examiner. The highest and lowest values were discarded, and the mean of the remaining three values was accepted as the true IOP. Before each IOP reading both eyes were examined with a slit-lamp for conjunctival hyperaemia, cells, and flare.

Day 1. No treatment was given, but a pressure curve was taken for both eyes every four hours between 0800 and 2000 and then at 0800 the next morning.

Day 2. After measuring the final pretreatment IOP a 30 µl eye drop containing 0·5 µg $PGF_{2\alpha}$-IE was applied to one eye of each patient at 0800. A new pressure curve was taken for both eyes. Previous studies with $PGF_{2\alpha}$-IE have shown a tendency to an initial increase in IOP. For that reason a first measurement was made 30 min after the first dose.

Table 1 *Mean IOP and IOP reductions (with SEM) in 30 patients before (day 1) and during (day 2) treatment with $PGF_{2\alpha}$-IE in one eye. (The final 0800 value on day 1 is the same as the first 0800 value on day 2). 0·5 µg $PGF_{2\alpha}$-IE was administered after the IOP measurements at 0800 and 2000 on day 2. For definition of IOP reductions and drug related IOP reductions see text*

Time	Treated eyes		Untreated eyes	
	IOP day 1	IOP day 2	IOP day 1	IOP day 2
0800	32·3 (1·7)	31·4 (1·6)	21·0 (1·1)	20·4 (1·0)
0830		32·1 (1·7)		19·6 (1·2)
1200	31·1 (1·6)	27·2 (1·6)	19·8 (0·9)	18·6 (0·9)
1600	31·2 (1·7)	26·7 (1·7)	19·6 (1·0)	18·8 (1·2)
2000	29·7 (1·5)	24·3 (1·4)	19·5 (1·0)	18·0 (1·0)
0800	31·4 (1·6)	24·8 (1·3)	20·4 (1·0)	19·7 (1·2)

Time	Reduction in intraocular pressure		
	Treated eyes	Nontreated eyes	Drug related
0800	0·9±0·7	0·6±0·4	
1200	3·8±0·7***	1·2±0·4**	2·7±0·7***
1600	4·5±0·6***	0·8±0·4	3·6±0·6***
2000	5·6±0·8***	1·5±0·4***	4·0±0·5***
0800	6·5±1·0***	0·7±0·6	5·8±0·7***

Asterisks indicate significance levels; *p<0·05, **p<0·01, ***p<0·001.

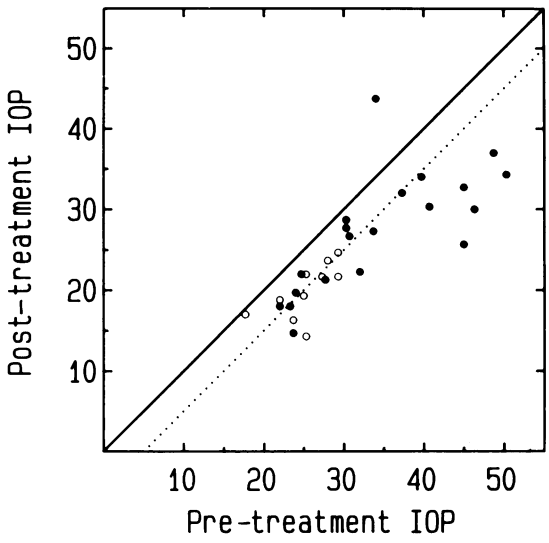

Fig. 1 *The effect of two doses of 0·5 µg $PGF_{2\alpha}$-IE on IOP. Pretreatment values, in mm Hg, are plotted on the abscissa, post-treatment on the ordinate. The value just before application of the first dose was chosen as pretreatment value, that is IOP at 0800 on day 2. Post-treatment IOP is the value 24 hours later, 12 hours after the second dose. The solid line indicates no effect. Points below the dotted line repesent eyes where the reduction in IOP exceeds 5 mm Hg. Closed circles: glaucoma capsulare. Open circles: glaucoma simplex.*

Apart from that the same time schedule was followed as on day 1. A second dose of 0·5 μg $PGF_{2\alpha}$-IE was applied after the 2000 IOP determination, and a final IOP was determined 12 hours later, at 0800 on day 3. The participants were questioned about local and systemic symptoms.

Days 3–8. For 10 patients treatment was continued for one week. Inclusion criteria for this second part of the study were no IOP readings above 30 mm Hg after treatment had been initiated and an IOP below 22 mm Hg on at least three of the five IOP measurements during treatment. Fourteen patients fulfilled these criteria; 10 of these were included in the second part of the study. They were treated with two daily doses of 0·5 μg in the glaucomatous eye for another six days. This subgroup consisted of one man and nine women, four of them with glaucoma capsulare and six with glaucoma simplex. On days 3 to 7 they were examined daily at 0800 and 2000 with slit-lamp biomicroscopy and IOP determinations. The drug was applied after the IOP determination. On day 8 the procedures for day 2 were followed, with a final IOP determination at 0800 on day 9, that is, 12 hours after the last dose.

EVALUATION OF EFFECT

The pretreatment IOP curve on day 1 was used as control, and the IOP reduction was defined as the change from baseline, that is, the difference (pretreatment IOP minus post-treatment IOP). Prostaglandins are rapidly inactivated in the lungs,[21] and a contralateral effect induced by systemically absorbed $PGF_{2\alpha}$ seems unlikely. However, a consensual IOP reduction has been described for several topical ocular hypotensive drugs.[22] To avoid including a possible general effect on IOP we also calculated the 'corrected', drug-related IOP reduction in the treated eye, defined as the difference in change from baseline between treated and untreated eye, that is, (the IOP reduction in the treated eye) minus (the IOP reduction in the untreated eye). The two-tailed Student's *t* test was used to find statistically significant differences. The results are presented as mean with SEM.

Results

Table 1 presents the IOP on days 1 and 2, the IOP reduction observed in treated and untreated eyes on day 2, and the corrected drug-related IOP reduction in the treated eye, as defined in the 'Methods' section. Four hours after the first dose a highly significant pressure reduction was observed in the treated eye, which remained significant when corrected for the fall in IOP observed in the untreated eyes. The effect slowly increased, and the largest effect was observed 12 hours after the second dose. Fig. 1 presents the IOP just before treatment (0800 on day 2) and 24 hours later, that is 12 hours after the second dose. All but one eye responded with a reduction in pressure. The reduction was more than 5 mm Hg in 18 eyes.

The IOP for the subgroup of patients treated for one week with 0·5 μg $PGF_{2\alpha}$-IE twice daily are presented in Fig. 2. Treatment reduced the IOP significantly, and the effect remained stable throughout the period of treatment. Before treatment the mean IOP ranged between 23·6 and 26·1 mm Hg, after treatment between 15·5 and 20·4 mm Hg. Table

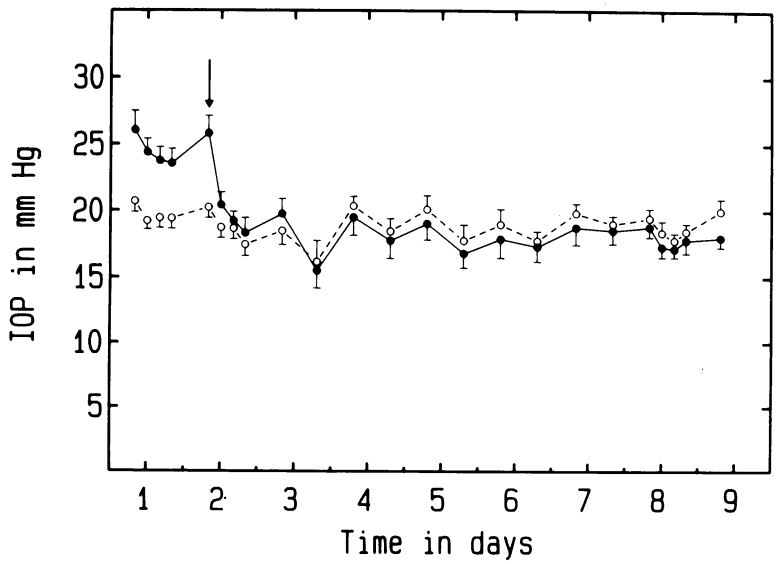

Fig. 2 *IOP (mean with SEM) in 10 patients treated with 0·5 μg $PGF_{2\alpha}$-IE twice daily in one eye for 7 days. The IOP was determined every four hours between 0800 and 2000 on days 1, 2, and 8, and at 0800 and 2000 on days 3–7. Treatment was initiated after the 0800 measurement on day 2 (arrow). The last dose was given at 2000 on day 8, and the final measurement was made 12 hours later. Closed circles: treated eye. Open circles: untreated eye.*

2 presents the reductions in IOP observed on days 2 and 8 in these patients. Also in this subgroup there is a significant reduction in IOP in the treated eye from four hours after the first dose, even when corrected for the fall in IOP in the fellow eye. Once again a slow increase in effect is observed during the first day of treatment, and the IOP reduction in the treated eye is more marked on day 8 than on day 2.

A separate analysis revealed that $PGF_{2\alpha}$-IE seemed to have similar effects on eyes with glaucoma simplex and glaucoma capsulare. Thus just before administration of the drug the IOP was 34·4 (SEM 2·1) mm Hg in 20 eyes with glaucoma capsulare and 25·3 (SEM 1·1) mm Hg in 10 eyes with glaucoma simplex. The drug related IOP reduction observed 24 hours later was 6·5 (SEM 1.0) mm Hg in glaucoma capsulare and 4·5 (SEM 0·5) mm Hg in glaucoma simplex, that is 19 and 18% of initial, untreated IOP respectively.

A slight to moderate conjunctival hyperaemia was observed in most patients in the treated eyes half an hour after administration of $PGF_{2\alpha}$-IE. With few exceptions the hyperaemia had disappeared 3–4 hours later. No flare or cells were observed.

About half the patients felt some discomfort in the treated eye for about one hour after application of the drug. This discomfort, mainly in the form of a foreign body sensation, was judged to be slight or moderate, and there was no tendency towards increased or decreased discomfort among the 10 patients that were treated for seven days. No systemic symptoms were reported.

Table 2 *Mean reductions in IOP (with SEM) in 10 patients on the first and seventh day of treatment (days 2 and 8) with 0·5 μg $PGF_{2\alpha}$-IE twice daily. For definitions of IOP reduction and drug related IOP reduction see text*

Time	*Treated eyes Day 2*	*Untreated eyes Day 2*	*Drug related Day 2*
0800	0·2 (1·0)	0·5 (0·4)	
1200	4·0 (0·9)**	0·5 (1·0)	3·5 (1·4)*
1600	4·5 (1·1)**	0·8 (0·7)	3·7 (0·9)**
2000	5·2 (0·7)***	2·0 (0·5)	3·3 (0·4)***
0800	6·1 (1·0)***	1·8 (1·0)	4·3 (0·6)***
Time	*Treated eyes Day 8*	*Untreated eyes Day 8*	*Drug related Day 8*
0800	7·0 (1·2)***	0·8 (0·9)	6·3 (1·0)***
1200	7·1 (1·2)***	0·8 (1·2)	6·3 (1·4)**
1600	6·6)0·8)***	1·6 (0·6)*	4·9 (0·6)***
2000	5·7 (1·2)***	0·9 (0·7)	4·8 (1·2)**
0800	7·8 (1·1)***	0·2 (0·9)	7·6 (0·7)***

Asterisks indicate significance levels: *p<0·05, **p<0·01, ***p<0·001.

Discussion

In a previous study on the effect of $PGF_{2\alpha}$-IE on the human eye a dose dependent reduction in IOP was observed, with 0·5 μg at the lower level of the dose response curve.[16] There was a tendency to increased IOP after 30 minutes and then a slow reduction that reached a maximum 8 to 12 hours after application of the drug. A similar pattern was observed in the present study. After a transient small increase the reduction slowly reached its maximum, and the results obtained in the group treated for one week indicate that the maximal effect may not even be reached during the first day of treatment. It must be kept in mind, however, that this subgroup was selected from patients who all responded with a reduction in IOP, and therefore a further increase in effect after the first day of treatment may be a biased observation.

0·1 μg $PGF_{2\alpha}$-IE had no effect on IOP in normal eyes,[16] and thus it seems unlikely that the decrease in IOP observed in the second, untreated eye is due to a true contralateral drug effect. In fact, a large part of that reduction was observed already before any drug had been applied to the eye. These patients had no previous experience with measurements of IOP, and an obvious possibility is that part of the reduction was due to accommodation to the examination techniques.

A slight conjunctival/episcleral hyperaemia was the only objective side effect observed in the present study. Large doses of prostaglandins may break down the blood-aqueous barrier, and flare and cells have been found in the anterior chamber of experimental animals.[14] No aqueous flare or cells were observed in the present study, which is in accordance with our previous experience with $PGF_{2\alpha}$-IE in human eyes. In normal eyes topical administration of 0·5–1·0 μg $PGF_{2\alpha}$-IE for one week has little or no effect on the permeability of the blood-aqueous barrier, even to a small molecule such as sodium fluorescein.[16]

The present study was designed to evaluate effects on IOP, and subjective side effects cannot be properly evaluated because local anaesthesia was given for IOP measurements before every drug administration. Among patients treated for one week about half experienced no subjective side effects, while the slight to moderate foreign body sensation reported by half of them seemed to be of the same order as in the previous study on healthy volunteers.[16]

In conclusion, topical $PGF_{2\alpha}$-IE reduces IOP in glaucomatous eyes in elderly patients. The maximal IOP reduction was about 20% of untreated IOP. The pattern of the IOP response and side effects were similar to those described previously for normal eyes in young healthy volunteers.

$PGF_{2\alpha}$-isopropylester eye drops were generously supplied by Pharmacia Ophthalmics AB, Uppsala, Sweden. The authors have no commercial or proprietary interest in $PGF_{2\alpha}$-IE eye drops.

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