PhXA34 – a prostaglandin $F_{2\alpha}$ analogue. Effect on intraocular pressure in patients with ocular hypertension

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Abstract

PhXA34, a prostaglandin analogue, was given topically to 40 patients with untreated ocular hypertension in a double masked randomised study. One single dose of 0.3, 1, 3, 10 μ g, or placebo (vehicle) was given to one eye of each patient. A dose related IOP reduction ranging from 11 to 35% was observed with a maximal effect with 3 and 10 μ g PhXA34. No hyperaemia was seen except after 10 μ g PhXA34, where a mild to moderate hyperaemia was seen from 8 hours with a duration of up to 24 hours. Mild foreign body sensation in the PhXA34-treated eye was noted by three patients. No cells or flare were seen.

Topical prostaglandin $F_{2\alpha}$ -isopropylester ($PGF_{2\alpha}$ -IE) reduces the intraocular pressure (IOP) both in normal and glaucomatous human eyes,¹⁻⁵ but side effects such as hyperaemia and discomfort are observed even after doses of $PGF_{2\alpha}$ -IE at the low range of the dose-response curve. An analogue of $PGF_{2\alpha}$ -IE, 13, 14-dihydro-15 (R,S)-17-phenyl-18, 19, 20-trinor $PGF_{2\alpha}$ -IE (PhXA34), is a potent ocular hypotensive agent in healthy eyes of young volunteers, and only minor side effects were observed after high doses.⁶ Thus PhXA34 improves the effect/side effect relationship compared with the parent compound $PGF_{2\alpha}$ -IE. The present report aims to study the dose-response with regard to IOP reduction and side effects of PhXA34 in a group of eyes with elevated IOP.

Design

The study was a double-masked and, placebo controlled in which one eye of 40 patients was randomised to one of five treatments: 0.3 μ g, 1 μ g, 3 μ g, 10 μ g PhXA34 or placebo (vehicle). There were eight patients in each group. The contralateral eyes did not receive any treatment but were otherwise subjected to the same procedures as the study eyes. The study protocol was reviewed and approved by the Ethics Committee of the Medical Faculty, University of Umeå and by the National Swedish Board of Health and Welfare. A signed informed consent was obtained from each patient.

PATIENTS

Patients were selected at the glaucoma unit of the Department of Ophthalmology. Inclusion criteria were age 30 to 80 years and untreated ocular hypertension with IOP more than 21 mm Hg on at least two occasions at the

outpatient glaucoma unit, normal optic disc, normal visual field, and normal open anterior chamber angle. If both eyes were eligible the eye with the higher IOP was chosen. Excluded were patients who received any medication known to affect the IOP and patients with any pulmonary, cardiovascular, metabolic, or other systemic disease judged by the investigator to be reason for exclusion. Also excluded were patients with ocular infection or inflammation active within 3 months, any corneal abnormality preventing reliable applanation tonometry, previous treatment with topical cholinomimetics, and any past intraocular operation including argon laser trabeculoplasty. Women with child-bearing potential were included only if reliable birth control was used: 32 women aged 41 to 78 years, and eight men aged 56 to 73 years were included.

STUDY DRUGS

The test solutions were administered from dropper bottles with a drop size of approximately 35 μ l. The vehicle contained polysorbate 80 (1.5 mg/ml) and benzalkonium chloride (0.2 mg/ml) in a phosphate buffer.

EXAMINATION SCHEDULE

The study was a single dose study carried out during 3 succeeding days with the last examination in the morning on day 3.

Day 1 (pretreatment day). A routine ocular examination including the optic disc and anterior chamber angle was performed. No drug was given but IOP measurements and examinations of the anterior chamber were performed four times: 7 am (t_0), 3 pm (t_8), 7 pm (t_{12}) and the next morning at 7 am (t_{24}). Each time the patients were asked about local and systemic symptoms.

Day 2 (treatment day). The drug was given topically in the selected eye after the IOP reading in the morning. Examinations of anterior chamber, IOP measurements, and registration of symptoms were performed as on day 1 but also 30 minutes after drug administration. Before each examination during the treatment day en face photographs were taken of the eyes of the patients.

Methods

IOP

The IOP was measured with a Goldmann applanation tonometer in a masked fashion (the scale of the tonometer was masked to the examiner). Three measurements were taken

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from each eye always starting with the right eye. The median value of the three readings was taken as the true IOP.

HYPERAEMIA

The degree of hyperaemia was determined from colour photographs and graded on a scale from 0 to 3 with seven steps, by comparing with four standard photographs covering the range from none to pronounced hyperaemia. The average of four independent and masked gradings determined the hyperaemia.

CELLS AND FLARE

The anterior chamber was examined by slit-lamp biomicroscopy. Flare was graded none, slight, moderate, or severe, and the number of cells, if any, were counted.

SYMPTOMS

Prior to IOP measurements the patients were asked in a standardised way about local and systemic symptoms. Symptoms and discomfort were graded mild, moderate, or severe.

DATA ANALYSIS

All IOP values are presented as means with 95% confidence intervals. The IOP values used for the dose-response curve (Fig 1) are based on the IOP determinations at *t*₈ and *t*₁₂. These two IOP values were averaged and the difference between average IOP day 1 (before treatment) and day 2 (after treatment) has been used as an estimate of drug effect for each patient. Also the differences in IOP for corresponding examination times on day 1 and day 2 have been calculated for all doses including placebo (see Table 2).

To find statistically significant differences between placebo effect and drug effects non-

Table 1 Forty patients were randomised to one of five different treatments with eight patients in each group. The baseline characteristics for the different treatment groups are shown

	Placebo	0.3 µg	1 µg	3 µg	10 µg
Number	8	8	8	8	8
Females	8	5	6	6	7
Males	0	3	2	2	1
Mean age	58.9	64.4	67.6	58.4	65.0
STD	10.4	6.6	5.6	12.2	8.0
Range	45-73	56-75	56-78	41-72	54-75
IOP	22.4	22.8	23.2	22.8	23.1
STD	2.54	3.83	4.40	2.47	2.95
Exfoliations	3	4	6	0	3
Right eyes	3	6	4	3	2
Left eyes	5	2	4	5	6

IOP is expressed as the mean of pretreatment day *t*₀, *t*₈, and *t*₁₂.

paired *t* tests have been used. The effect on IOP expressed as the area under the curve for the differences in IOP day 1 and day 2 for each treatment group has been calculated using a simple numerical estimation of area by the trapezoidal rule.⁷

The contralateral eyes were a mixed group of normal eyes and eyes with ocular hypertension, and they have not been included in the analysis.

The estimated hyperaemia is based on the difference between the maximum score on day 2 and the score before examination and IOP measurement at *t*₀ day 2.

Results

All patients completed the study. The results of randomisation are shown in Table 1. Figure 1 shows the average IOP reductions (mean with 95% confidence interval) for placebo and increasing doses of PhXA34 8 and 12 hours post-dose.

Table 2 IOP in the study eyes for the different treatment groups day 1 and day 2

Time	Day 1	Day 2	Change in IOP
Placebo			
0	24.9 (23.2-26.6)	25.8 (22.5-29.0)	-0.9 (2.0-3.8)
0.5		26.8 (24.0-29.5)	-1.0 (-0.1-1.9)
8	20.8 (19.2-22.3)	20.1 (18.5-21.8)	0.6 (1.6-0.4)
12	21.6 (20.2-23.0)	20.6 (17.9-23.4)	1.0 (2.9-0.9)
24	25.8 (22.5-29.0)	22.9 (20.2-25.5)	2.9 (5.4-0.4)
PhXA34 0.3 µg			
0	24.9 (22.1-27.6)	23.9 (20.1-27.7)	1.0 (3.4-1.4)
0.5		25.1 (21.8-28.5)	-1.3 (1.2-3.7)
8	20.6 (17.7-23.5)	18.9 (16.9-20.8)	1.8 (3.7-0.0)
12	23.0 (19.8-26.2)	19.9 (16.0-23.8)	3.1 (5.1-1.2)
24	23.9 (20.1-27.7)	21.9 (19.3-24.5)	2.0 (4.7-0.7)
PhXA34 1 µg			
0	25.8 (20.5-31.0)	24.5 (21.1-27.9)	1.3 (4.3-1.8)
0.5		23.4 (18.4-28.4)	1.1 (3.2-1.0)
8	22.0 (20.5-23.5)	17.1 (14.8-19.4)	4.9 (6.5-3.2)
12	21.9 (19.3-24.4)	16.4 (13.1-19.7)	5.5 (8.6-2.4)
24	24.5 (21.1-27.9)	21.5 (17.4-25.6)	3.0 (5.5-0.5)
PhXA34 3 µg			
0	24.5 (22.1-26.9)	23.5 (20.8-26.2)	1.0 (3.2-1.2)
0.5		24.0 (22.1-25.9)	-0.5 (2.1-3.1)
8	21.8 (20.6-22.9)	15.0 (13.0-17.0)	6.8 (8.4-5.1)
12	22.0 (20.2-23.8)	14.4 (11.8-16.9)	7.6 (9.4-5.8)
24	23.5 (20.8-26.2)	20.3 (17.7-22.8)	3.3 (5.2-1.3)
PhXA34 10 µg			
0	24.4 (21.2-27.6)	24.0 (20.8-27.2)	0.4 (2.5-1.8)
0.5		24.9 (21.4-28.4)	-0.9 (1.0-2.8)
8	22.5 (21.0-24.0)	15.5 (14.2-16.8)	7.0 (8.1-5.9)
12	22.4 (20.1-24.7)	14.5 (13.7-15.3)	7.9 (10.5-5.2)
24	24.0 (20.8-27.2)	18.6 (17.2-20.0)	5.4 (8.1-2.7)

The values are means in mm Hg with 95% confidence interval. The drug was given topically shortly after *t*₀ (7 am) on day 2. The change in IOP is calculated as IOP day 1 minus IOP day 2 at the corresponding time of the day except for the *t*_{0.5} value which is compared with the IOP just before drug application (*t*₀ on day 2). IOP values *t*₂₄ on day 1 are identical to the values *t*₀ on day 2, but listed to make comparison easier. Negative values indicate an increase in IOP and positive values indicate a reduction in IOP. There were eight patients in each group.

Figure 1 The effect on IOP and conjunctival hyperaemia of four single doses of PhXA34 and placebo. The values used to express the IOP reduction for each dose are based on the IOP determinations at *t*₈ and *t*₁₂. These two values were averaged and the difference between average IOP day 1 (before treatment) and average IOP day 2 (after treatment) was used as an estimate of drug effect for each patient. Hyperaemia was estimated for each patient as the difference between maximum score on day 2 (after treatment) and the registration at *t*₀ day 2. Closed circles: mean IOP reduction with 95% confidence interval; open circles: mean hyperaemia.

Table 3 The degree of hyperaemia in the study eyes. The procedures used for the grading are described in the text

Treatment time	Grade of hyperaemia						
	0	0.5	1	1.5	2	2.5	3
<i>Placebo</i>							
* 0	0	5	2	0			
* 8	2	4	1	0			
* 12	1	3	3	0			
* 24	3	1	1	2			
<i>PhXA34 0.3 µg</i>							
0	1	3	4	0			
* 8	3	3	1	0			
12	2	3	3	0			
24	4	2	1	1			
<i>PhXA34 1.0 µg</i>							
* 0	0	5	2	0			
* 8	0	3	4	0			
* 12	0	3	2	2			
* 24	1	2	3	1			
<i>PhXA34 3.0 µg</i>							
* 0	1	3	3	0			
* 8	0	2	3	1			
* 12	1	2	3	1			
* 24	2	5	0	0			
<i>PhXA34 10.0 µg</i>							
0	0	4	4	0	0		
8	0	0	3	4	1		
12	0	0	2	4	2		
24	0	0	5	2	1		

The numbers in each column indicate the number of eyes with the specific grade of hyperaemia.
The drug was given shortly after *t*₀.
*Notifies that the number of photographs in that row is 7.

They were 0.8 (−0.7–2.3), 2.4 (0.4–4.5), 5.4 (3.0–7.8), 7.0 (5.3–8.7) and 7.8 (5.8–9.8) mm Hg. The corresponding reductions expressed as a percentage of IOP on day 1 were 4%, 11%, 25%, 32% and 35%.

When compared with placebo 1, 3, and 10 µg PhXA34 were significantly better in reducing the IOP whereas 0.3 µg was not significantly changed from placebo: 0.3 µg *p*<0.1, 1 µg *p*<0.002, 3 µg *p*<0.001, 10 µg *p*<0.001; (*t* test for two independent means with pooled estimate of common variance).

Table 2 presents the IOP values on day 1 and day 2 for the five different treatment groups including the differences in IOP between the 2 days.

The change in IOP for the different treatment groups can also be expressed as area under the curve and these values were for placebo and increasing doses of PhXA34: 24 (−15–65), 42 (−12–96), 94 (38–153), 118 (72–164), 132 (82–184). Values are means in mm Hg hours with upper and lower limits for the 95% confidence interval.

IOP was measured 30 minutes after the drug application on day 2 and at that time no significant effect on IOP was found for any dose of PhXA34.

No discomfort was felt by any patient before drug application, but mild discomfort was noted by a total of seven patients at some time during the remaining part of day 2. Symptoms in both eyes with no difference between the two eyes were felt by three patients. Discomfort in the treated eye only, mainly in the form of a mild foreign body sensation, was reported by four patients: one placebo treated, two treated with 1 µg PhXA34, and one treated with 3 µg PhXA34. Additionally, headache was reported by one patient treated with placebo.

No significant difference in hyperaemia between study eyes and contralateral eyes was

present in any treatment group before drug application. No hyperaemia was observed for any dose 30 minutes after drug application, and hyperaemia was practically absent for doses lower than 10 µg. This dose however produced observable hyperaemia grade 1.5–2 in most patients (Table 3). Photographs were not achieved from three patients due to camera problems. These patients were treated with placebo, 1 µg, and 3 µg PhXA34 respectively, and the 8-hour photograph from a patient treated with 0.3 µg PhXA34 was not possible to grade. No flare or cells were seen in the anterior chamber.

Discussion

The result of randomisation did not show any important differences except for an uneven distribution of the 16 eyes with exfoliations. The high frequency of patients with exfoliations reflects the expected distribution in a group of patients with ocular hypertension in the northern part of Sweden.

A prior study has shown a clear dose-related IOP reduction in normal eyes.⁶ A dose-related response was also found in this study with regard to IOP reduction; 3 and 10 µg PhXA34 seem to be almost equipotent with regard to IOP reduction based on average IOP reduction 8 and 12 hours post dose, but 10 µg appears more potent if the IOP reduction 24 hours after the dose is included as in the values expressed as area under the curve. The 8 and 12 hours average IOP reduction was chosen as the primary variable for this dose-response study because it is known from prior studies that the maximal effect is observed within this period for most doses. In this study the maximal effect is seen 12 hours after the dose for all doses of PhXA34, and the inclusion of the 8-hour values therefore results in a slight underestimate of the peak IOP reduction.

In the contralateral eyes we observed only minor fluctuations in IOP with a tendency towards a slight IOP reduction of normally less than 1 mm Hg on day 2, and these changes seemed to be completely unrelated to the dose given in the study eye. Hyperaemia was negligible for doses lower than 10 µg PhXA34 suggesting that the dose-response curve for hyperaemia is displaced to the right of the IOP dose-response curve. This is in contrast to the hyperaemia observed after PGF_{2α}-IE where all effective doses caused some hyperaemia. There is also a difference in the timing of the hyperaemia since none was visible for any dose of PhXA34 30 minutes after application, while PGF_{2α}-IE produces maximal hyperaemia within the first hour. High doses of PGF_{2α}-IE also caused an initial increase in IOP, probably due to intraocular vasodilation, something that was not observed even with 10 µg PhXA34.

In summary PhXA34 is a potent ocular hypotensive agent also in patients with ocular hypertension, where one topical dose of 3 µg reduce IOP about 32% 8–12 hours after application without clinically significant side effects.

PhXA34 eye drops and project support were supplied by Kabi Pharmacia Ophthalmics AB, Uppsala, Sweden. The authors have no commercial or proprietary interest in PhXA34 eye drops.

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FIFTY YEARS AGO

Paper Salvage

Our readers will probably have noticed the slight difference in texture and tint of the paper used for printing the Journal since the beginning of this year. Our stock of paper came to an end in December last and like everybody else we have had to make do with what the controller allows us. In after years it may be of interest as dating some of the War years. Deterioration in quality of paper during war is no new thing. Exactly the same happened in the Napoleonic struggle. Much of the paper used in the earlier years of the last century was very poor in quality and no one now-a-days would dream of reading such a thing as the first edition of Waverley (published 1814), if he could get a later edition.

It behoves us all to contribute as much as we can to the paper salvage campaign. For ourselves we almost tremble to think of the numbers of galleys of back numbers which we have sent to the pulping machine. Old books, old letters, old receipts and

paper of every kind are badly needed. It has been rather a wrench to cast out copies of old text-books which we used in the days of our studentship. Some of these were at least forty years out of date but had a sentimental interest to us.

Those who were brought up in Victorian days will be aware of the hoarding propensities of parents in the matter of family and other letters. A great many, but not all, of these are very suitable for salvage. Young hopeful's reiterated appeals from school for a hamper or a new cricket bat or even a modest half-a-crown are not worth keeping, but no one in his senses would destroy letters by eminent hands. If, in going through bundles of old correspondence, one lights upon a letter, for instance, from the poet Wordsworth to one's own grandfather it will be wise to preserve it, for its value may appreciate in post-war times.

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