Intraocular Pressure Reduction With PhXA34, a New Prostaglandin Analogue, in Patients With Ocular Hypertension

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• In a randomized, double-masked, parallel study, one drop of 0.003% (1 μg; n=9) or 0.01% (3 μg; n=10) PhXA34, a new phenyl-substituted prostaglandin $F_{2\alpha}$ analogue (13,14-dihydro-15[R,S]-17-phenyl-18,19,20-trinor-prostaglandin $F_{2\alpha}$-1-isopropyl ester), or its vehicle (n=10) was applied topically twice daily for 6 days to one eye in each of 29 patients with ocular hypertension. Compared with either baseline, contralateral, or vehicle control values, PhXA34 caused a significant ($P<.001$) dose-dependent reduction of intraocular pressure. The reduction lasted at least 12 hours after each drop and 24 to 48 hours after the last drop, with a significant ($P<.0001$) mean±SEM reduction of as much as 10±1 mm Hg (40%). Conjunctival hyperemia was not produced by 0.003% PhXA34, but was noted in some eyes treated with 0.01% PhXA34, and after repeated tonometry with either concentration. The prostaglandin analogue did not produce clinically obvious miosis, anterior chamber flare or cellular response, or any subjective adverse effects. PhXA34 is a potent, effective, and well-tolerated ocular hypotensive agent based on our results in this small, short-term study. Its potential as a new drug for glaucoma therapy warrants further investigation in long-term, larger studies.

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Several prostaglandins are effective ocular hypotensive agents when applied topically to normotensive or glaucomatous eyes in experimental animals[1,2] and in humans.[2,3] Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) tromethamine salt[4,5] and $PGF_{2\alpha}$-1-isopropyl ester ($PGF_{2\alpha}$-IE),[6-8] a pro-drug with greater potency,[9] effectively reduce intraocular pressure (IOP) in normal volunteers and patients with glaucoma. This reduction of IOP is additive to that produced by timolol maleate in patients with ocular hypertension or glaucoma.[10,11] However, the tromethamine salt[4,5] causes conjunctival hyperemia and local irritation, which is reduced, but not eliminated, when the isopropyl ester pro-drug form of $PGF_{2\alpha}$ is used.[6,7]

PhXA34 (13,14-dihydro-15[R,S]-17-phenyl-18,19,20-trinor-prostaglandin $F_{2\alpha}$-1-isopropyl ester) is a mixture of the two epimeric forms of a new phenyl-substituted $PGF_{2\alpha}$ analogue pro-drug. Compared with $PGF_{2\alpha}$-IE, PhXA34 produces substantially less conjunctival hyperemia in rabbits, and does not irritate cat or monkey eyes.[12] When given twice daily for 5 days in laser-induced glaucomatous monkey eyes, PhXA34 reduces IOP without tachyphylaxis or intraocular side effects.[13] Like $PGF_{2\alpha}$-IE,[14,15] PhXA34 acts primarily by increasing uveoscleral outflow in monkeys.[16] In normotensive volunteers, PhXA34 recently was found to reduce IOP with fewer local adverse side effects than other prostaglandins and their analogues.[17]

The present study evaluates the ocular hypotensive potency and side effects of twice daily topical application for 6 days of two concentrations of PhXA34 in patients with ocular hypertension.

PATIENTS AND METHODS

Patient Selection

To be eligible for the study, at least one eye of each subject from the patient population at Mt Sinai Medical Center (New York, NY) had to meet the following criteria: (1) mean IOP of 22 mm Hg or higher without treatment or 17 mm Hg or higher with treatment, based on the last several IOPs in each patient's record; (2) mean IOP of at least 20 mm Hg on diurnal testing on the baseline day after washout of all medications for glaucoma; (3) nonocculdable anterior chamber angle; and (4) no glaucomatous visual field defects as determined by Goldmann perimetry on the screening examination. If subjects had been receiving glaucoma therapy, their medications were discontinued at least 3 weeks before the study.

Patients were excluded from the study for any one of the following reasons: (1) younger than 21 years; (2) currently pregnant, considering pregnancy, or nursing an infant; (3) current use of any ocular medications other than for glaucoma; (4) an established diagnosis of secondary glaucoma, including exfoliation or pigmentary dispersion syndrome; (5) narrow angles or angle closure glaucoma; (6) prior ocular surgery or laser therapy; or (7) a history of medical noncompliance or unreliability.

Protocol

After proper informed consent and approval by the Mt Sinai Institutional Review Board, a medical history from each subject was obtained, including a list of all systemic medications. In addition, pulse rate and blood pressure were measured. A complete ophthalmologic history and examination were done on each patient within 4 weeks of the onset of the study, including best-corrected Snellen visual acuity, Goldmann visual fields, assessment of motility, gonioscopy, and direct and indirect ophthalmoscopic examination of the optic nerve-

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Table 1.—Times of Measurements, Evaluation, and Observations Before, During, and After Treatment*

Measurement	Day Assessed†	Time of Day 7:30 AM	8:30 AM	10 AM	Noon	2 PM	4 PM
Conjunctival hyperemia photographs‡	5	X	...	...	...	X	X
Subjective side effects‡§	0-2, 5, 6	X	X	X	X	X	X
Pupillary diameter	0, 5, 6	X	X	X	X	...	...
Conjunctival hyperemia‡	0-2, 5-8	X	X	X	X	X	X
Slit-lamp examination‡‖	0-2, 5-8	X	...	X	X	X	X
Intraocular pressure	0-2, 6-8	X	X	X	X	X	X
Pulse rate	0, 5, 6	...	...	...	...	X	...
Blood pressure	0, 5, 6	...	...	...	...	X	...

*Beginning 1 day after baseline day (day 0), treatment was administered twice daily at 8 AM and 8 PM on days 1-5 and once (last dose) at 8 AM on day 6 (11 doses).

†Assessment on days 7 and 8 was performed at 8 AM only, at 24 and 48 hours, respectively, after the last dose.

‡Evaluated on a relative scale as follows: 0 indicates no reaction; 0.5, barely detectable; 1, mild; 2, moderate; and 3, severe.

§Including any side effect spontaneously reported. On day 5, patients were specifically asked about burning, stinging, foreign-body sensation, pain, photophobia, visual disturbances, palpitations, wheezing, and shortness of breath.

‖Includes assessment of anterior chamber flare and cellular response.

head and fundus. Factors that were assessed on the screening examination and also evaluated more frequently throughout the study included pupillary diameter measured with a millimeter ruler under standard room illumination, external and slit-lamp biomicroscopic examinations, and determination of IOP with a calibrated Goldmann applanation tonometer (using topical 0.5% proparacaine hydrochloride and fluorescein strips).

On the baseline day, all of the factors indicated in Table 1 were assessed. The following day, one drop (approximately 35 μL) of 0.003% or 0.01% (1-μg or 3-μg free-acid equivalent, respectively) of PhXA34 or its vehicle was applied topically to one eye in each of 30 subjects in a randomized, double-masked fashion at 8 AM and 8 PM each day for 5 consecutive days, and at 8 AM only on the 6th day, for a total of 11 doses. The vehicle consisted of 0.15% polysorbate 80, 0.02% benzalkonium chloride, 0.05% disodium dihydrogen phosphate hydrate, 0.6% disodium hydrogen phosphate dihydrate, and 0.4% sodium chloride in water. The contralateral control eyes were not treated. For each patient, the eye with the higher mean IOP on the baseline day received treatment with PhXA34 or the vehicle. Coded bottles numbered 1 through 30 were supplied by the manufacturer (Kabi Pharmacia Ophthalmics, Uppsala, Sweden) and were randomly assigned to each of the 30 patients. Neither the examiners nor the subjects were informed as to the identity of the drop received during the course of the study. On completion of the study, the code was broken by the manufacturer.

On the 1st, 2nd, 5th, and 6th days of treatment, and 24 and 48 hours after the last dose, the factors specified in Table 1 were recorded at the same time of day as had been done on the baseline day. Of note is that on day 5, subjective side effects, conjunctival hyperemia (including photographs of the bulbar conjunctiva), and slit-lamp biomicroscopic examination of anterior segment morphology, aqueous flare, and anterior chamber cellular response were determined without any tonometry or topical anesthetic.

Compliance was encouraged and monitored by careful counseling, questioning, and home record-keeping. Patients were also asked to record the date and time of administration of each dose on specially designed cards, as well as any subjective side effects. The two-tailed, paired t test was used for statistical evaluation of differences between treatment and baseline values and between treatment and contralateral control values. The two-tailed, unpaired t test was used to evaluate differences between PhXA34 and vehicle-treated eyes.

Table 2.—Demographic Characteristics of Patients (n=10 for Each Group)*

	Group: Vehicle	0.03% PhXA34	0.01% PhXA34
Sex			
M	4	5	5
F	6	5	5
Race			
Black	6	4	6
Hispanic	2	2	4
White	1	3	0
Indian	1	1	0
Iris color			
Brown	9	8	10
Blue	1	1	0
Green	0	1	0
Age, y			
Mean±SEM	63±3	66±4	68±4
Range	46-72	41-83	39-75
Treated eye			
Right	6	5	6
Left	4	5	4
Previous glaucoma medications			
Number			
No treatment	2	2	2
1 type	5	1	6
2 types	0	6	2
3 types	3	1	0
Type			
β-blocker	6	8	7
Adrenergic agonist	4	5	1
Cholinergic agonist	4	2	2
Carbonic anhydrase inhibitor	0	1	0

*Values represent numbers of patients, except for age.

Demographics

No significant difference occurred among the three treatment groups in regard to sex, race, iris color, age, or treated eye (right vs left), although the previous medical therapies appeared to be less evenly distributed (Table 2). Of the 30 patients initially enrolled, all but one completed the study. During the first day of the study, a 72-year-old white man with a

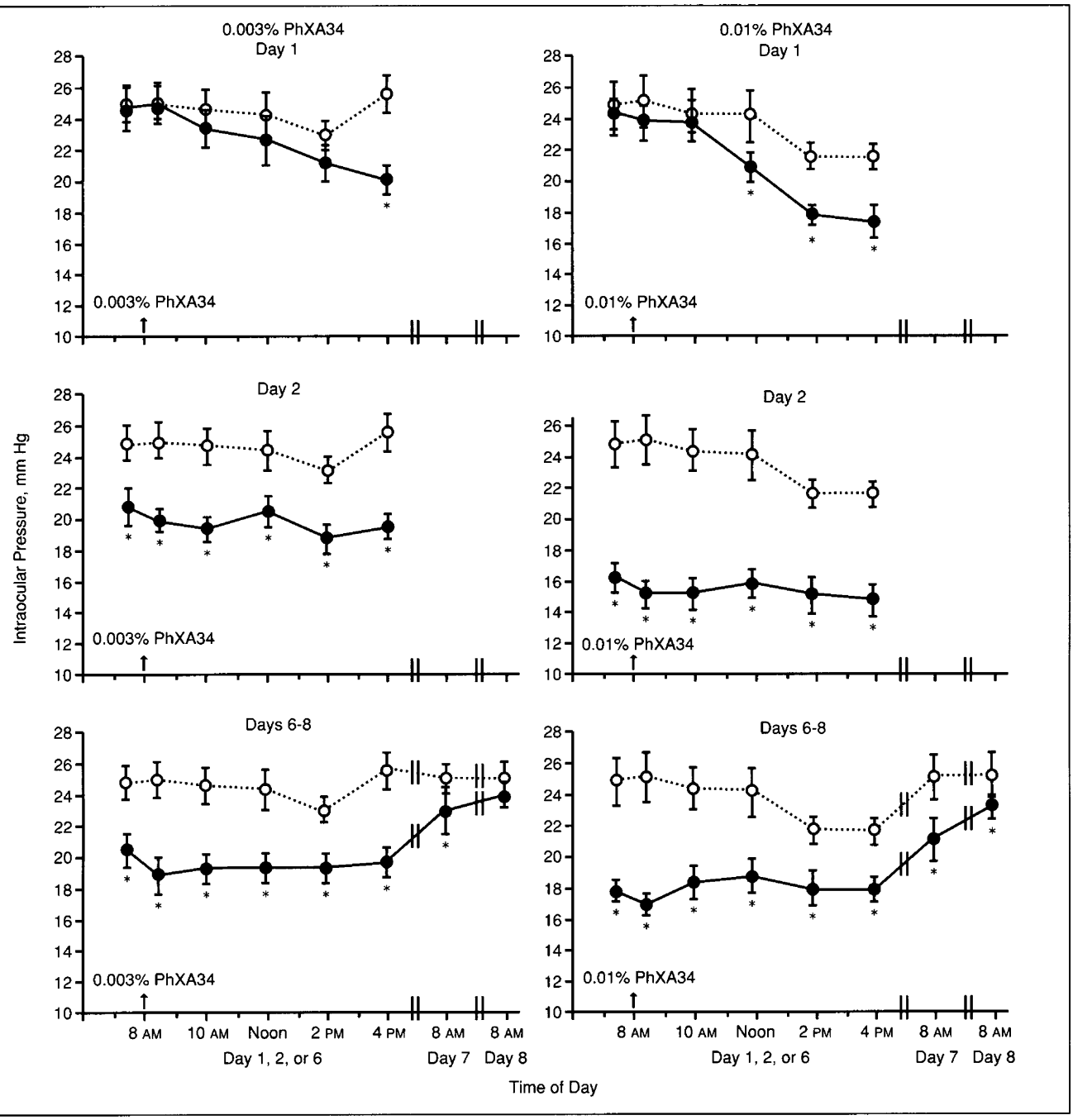

Fig 1.—Intraocular pressure on the 1st, 2nd, and 6th through 8th days of treatment with 0.003% or 0.01% PhXA34. Solid circles indicate values in eyes receiving treatment with the prostaglandin given twice daily at 8 AM and 8 PM for 6 days (11 doses) in nine (0.003% group) or 10 (0.01% group) patients with ocular hypertension compared with baseline measurements (open circles) taken on the day before treatment. The values obtained at 7:30 AM on days 2 and 6 were taken 12 hours after the previous dose. The values obtained at 8 AM on days 7 and 8 were taken 24 and 48 hours, respectively, after the last dose. The circles and bars represent means and SEMs, respectively; and asterisks, measurements were significantly ($P<.05$) different from baseline values using two-tailed, paired t tests.

history of two previous myocardial infarctions, who had been assigned to the 0.003% PhXA34 group, dropped out because of chest pain.

RESULTS

Intraocular Pressure

Compared with baseline measurements, PhXA34 caused a significant ($P<.001$), dose-dependent reduction of IOP beginning at 4 and 8 hours after the first applications of the 0.01% and 0.003% doses, respectively, and lasting throughout the 6 days of treatment (Fig 1). On day 2 of treatment, the mean IOP was reduced from pretreatment baseline values by 4 to 6 mm Hg (20% to 25%) with 0.003% PhXA34 and by 7 to 10 mm Hg (30% to 40%) with 0.01% PhXA34 (Fig 1). On this day, the IOP reduction, compared with baseline values, was significantly ($P<.001$) greater for eyes treated with the 0.01% concentration than for those treated with 0.003% PhXA34 (Fig 1). On day 6 of therapy, the mean IOP was reduced by 4 to 8 mm Hg with either concentration (Fig 1). The IOP reduction was significantly ($P<.001$) less on day 6 than on

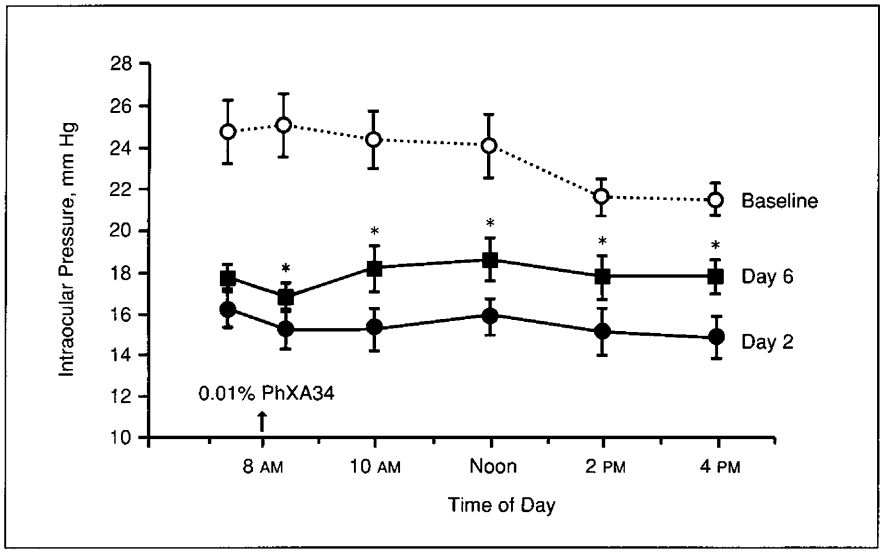

Fig 2.—Intraocular pressure before and after the 3rd (solid circles) and 11th (squares) applications of 0.01% PhXA34 on the 2nd and 6th days of treatment, respectively, in 10 patients with ocular hypertension compared with baseline measurements (open circles). The measurements at 7:30 AM were taken 12 hours after the previous dose. The circles and bars represent means and SEMs, respectively; and asterisks, measurements were significantly ($P<.05$) different on day 6 vs day 2 using two-tailed, paired t tests.

day 2 of treatment for the 0.01% concentration only (Fig 2). Compared with baseline values, a significant ($P<.001$) mean reduction of 4 to 9 mm Hg persisted 12 hours after each dose with either concentration. A significant ($P<.05$) IOP reduction was maintained even 24 hours after the last dose with either concentration, and as much as 48 hours after the last dose with the higher concentration of PhXA34 (Fig 1). The IOP of each PhXA34-treated eye was reduced by at least 6 mm Hg compared with baseline values at some time during the course of treatment, with one eye showing a reduction of as much as 19 mm Hg. Neither vehicle-treated nor contralateral untreated control eyes showed a consistently significant reduction of IOP compared with baseline values.

Conjunctival Hyperemia

Eyes treated with PhXA34 showed a significant, dose-dependent conjunctival hyperemic response during the first 2 days of treatment when the eyes underwent repeated tonometry and topical anesthetic application (Fig 3). In eyes receiving the higher concentration of PhXA34, conjunctival hyperemia reached a maximum on day 2 of treatment (Fig 3), which was the third consecutive day of repeated tonometry. During the 5th day of therapy, when assessment of conjunctival hyperemia was made and photographs were taken, but tonometry was not performed, 0.003% PhXA34 did not produce observable conjunctival hyperemia (Fig 3). However, with the 0.01% concentration during the 5th day, more conjunctival hyperemia was noted in treated than in contralateral control eyes in five of the 10 patients, with a significant ($P<.01$) mean difference noted 4 to 8 hours after application (Fig 3). On day 5 of treatment, no eyes had more than mild conjunctival hyperemia, except for a single patient who had moderate hyperemia of equal magnitude in both the PhXA34-treated and contralateral untreated eyes.

Subjective Side Effects

Seven of the patients in the vehicle-treated group, five in the 0.003% PhXA34 group, and six in the 0.01% group reported more subjective side effects in their treated than in their untreated eyes at least once during the 6 days of treatment. These side effects included mild foreign-body sensation, discomfort, burning, and stinging. None of these subjective side effects was unique to the PhXA34-treated compared with vehicle-treated eyes. No patient requested discontinuation of the medications or withdrawal from the study.

Other Evaluated Factors

Compared with contralateral control eyes, vehicle-treated eyes, or baseline mesurements, PhXA34 did not significantly alter the pupillary diameter, anterior chamber flare or cellular response, pulse rate, or blood pressure.

Patient compliance appeared to be good throughout the course of the study as revealed by the home record-keeping cards and by specific questioning on the days of examination. One patient inadvertently applied 0.01% PhXA34 to both eyes on the evening of day 4 of treatment. One patient taking vehicle missed the 8 PM treatment on day 2, and one patient taking 0.01% PhXA34 missed the 8 PM treatment on day 1.

COMMENT

Similar to previous clinical results with $PGF_{2\alpha}$-IE,[6-8] PhXA34 causes a highly significant and prolonged reduction of IOP. As with the long-lasting ocular hypotensive effect after discontinuation of nonselective β-adrenergic blocker therapy,[18,19] a significant residual effect persisted for at least 2 days after the last application of 0.01% PhXA34. The magnitude of the IOP reduction (20% to 40%) was comparable with that achieved with nonselective β-blocker therapy.[18] All patients treated with PhXA34 showed a hypotensive response without exception. Unlike after application of β-blockers or cholinergic agonists, 4 to 8 hours was required before a significant reduction of IOP occurred after the first application of PhXA34. This delayed effect may limit its clinical use for achieving a rapid IOP reduction in some cases of acute glaucoma. Compared with other prostaglandin analogues used in clinical trials,[20-22] PhXA34 produced a similar or more pronounced reduction of IOP, but unlike PGE_2 and PGD_2 derivatives or their analogues,[20,22] PhXA34 did not cause an initial rise in IOP in humans.

Whereas the 0.003% concentration of PhXA34 produced a similar reduction of IOP on the 2nd and 6th days of treatment, the 0.01% concentration reduced IOP significantly more on day 2 than on day 6 of therapy in this study. Although partial tachyphylaxis with the higher concentration is a possibility, the more pronounced reduction of IOP on day 2 might have been due to enhanced penetration of PhXA34 from repeated proparacaine applications and tonometry. Day 2 of therapy was preceded by 2 consecutive days of repeated tonometry measurements, whereas day 6 was preceded by 3 days without tonometry.

The conjunctival hyperemia observed with PhXA34, even with the higher dose, was considerably less than previously reported by our group[6] and others[7] for $PGF_{2\alpha}$-IE, or for other eicosanoids tested in clinical trials.[4,5,20,22,23] In addition, a difference in time course was apparent with maximal conjunctival hyperemia occurring at 30 to 60 minutes after topical application of $PGF_{2\alpha}$-IE,[6,7] but at 6 to 8 hours after PhXA34. The 0.003% concentration of

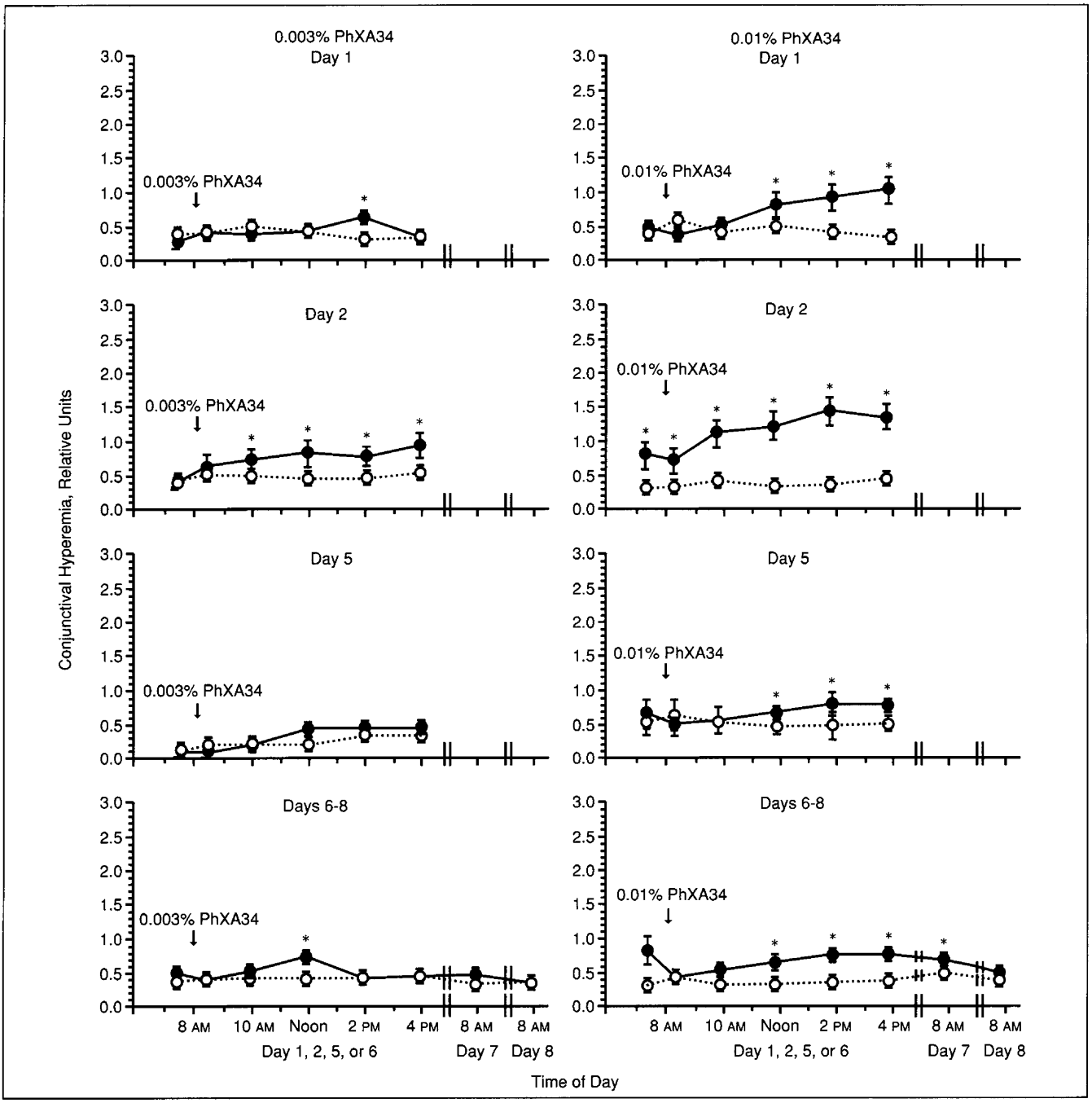

Fig 3.—Relative conjunctival hyperemic response to 0.003% or 0.01% PhXA34 (solid circles) compared with contralateral untreated values (open circles) on the 1st, 2nd, 5th, and 6th through 8th days of treatment in nine (0.003% group) or 10 (0.01% group) patients. Conjunctival hyperemia was evaluated on a relative scale as follows: 0 indicates no reaction; 0.5, barely detectable; 1, mild; 2, moderate; and 3, severe. Although patients underwent repeated tonometry and received topical proparacaine hydrochloride on the 1st, 2nd, and 6th days, day 5 values were assessed 3 days after the last application of proparacaine and tonometry. The circles and bars represent means and SEMs, respectively; and asterisks, values were significantly ($P<.05$) different between treated and contralateral controls using two-tailed, paired t tests.

PhXA34 produced significant conjunctival hyperemia only on days when repeated tonometry was performed. Therefore, 0.003% PhXA34 may exacerbate the conjunctival hyperemic response caused by repeated topical application of proparacaine[24] and/or tonometry, but does not by itself cause significant conjunctival hyperemia under normal conditions.

Unlike $PGF_{2\alpha}$-IE, which causes mild irritation, foreign-body sensation, discomfort, burning, and stinging,[6,7] PhXA34 did not produce any such sensory side effects. Furthermore, PhXA34 did not produce aqueous flare, an anterior chamber cellular response, or any other adverse effects as determined by slit-lamp biomicroscopy. In contrast, $PGF_{2\alpha}$ tromethamine salt, PGD_2, PGE_2, and/or their analogues produced significant itching, foreign-body sensation, burning, pain, photophobia, irritation, and/or headaches.[4,5,20,22] Therefore, the chemical modifications introduced in PhXA34 have successfully eliminated the nociceptive and irritative effects caused by naturally occurring prostaglandins or by their previous modifications.

In a study conducted in Sweden on blue-eyed normal volunteers, PhXA34 produced a dose-dependent IOP reduction.[17] The present study demonstrates that the same doses of PhXA34 also effectively reduce IOP in ocular hypertensive patients of mixed racial and ethnic backgrounds, including patients with heavy ocular pigmentation. These results suggest that competitive binding with melanin either does not occur or does not alter the hypotensive effect of PhXA34 at the concentrations tested. Similar to findings with other medications used in glaucoma therapy, the present study demonstrates that the efficacy of PhXA34 is greater in patients with ocular hypertension than in normotensive volunteers.[17] In normal volunteers, PhXA34 did not significantly alter aqueous flow, but increased tonographic outflow facility,[17] similar to what has been observed in clinical studies with $PGF_{2\alpha}$-IE.[6,7,25] Since the reduction of IOP cannot be totally accounted for by the increase in tonographic outflow facility, PhXA34, like $PGF_{2\alpha}$-IE, presumably acts primarily by increasing uveoscleral outflow in humans,[17] as it does in monkeys.[16] This mechanism of action may account for its delayed effect of 4 to 8 hours after its first application.

Our results demonstrate that PhXA34 is a potent, effective, and well-tolerated ocular hypotensive agent in ocular hypertensive patients of mixed racial and ethnic origins. Further studies are required to determine its long-term safety and efficacy and to evaluate its additivity with other medications used in glaucoma therapy. This phenyl-substituted $PGF_{2\alpha}$ analogue shows great promise as a clinically useful ocular hypotensive agent.

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