Effect of Latanoprost or 8-iso Prostaglandin E<sub>2</sub> Alone and in Combination on Intraocular Pressure in Glaucomatous Monkey Eyes

Rong-Fang Wang, MD; Steven M. Podos, MD; Janet B. Serle, MD; Thomas W. Mittag, PhD; F. Ventosa, MD; Bernard Becker, MD

Objective: To evaluate the possible additivity of the effects of latanoprost and 8-iso prostaglandin E<sub>2</sub> (8-iso PGE<sub>2</sub>) on intraocular pressure (IOP) in monkey eyes with laser-induced glaucoma.

Methods: The IOP was measured hourly for 6 hours beginning at 9:30 AM on day 1 (baseline day), days 6 and 7 (single-agent therapy), and days 13 and 14 (combination therapy with both agents). Following 1 day of baseline measurement, 4 monkeys with unilateral glaucoma received monotherapy twice daily with either 1 drop of 0.005% latanoprost, or 0.1% 8-iso PGE<sub>2</sub>, 25 µL, at 9:30 AM and 3:30 PM from days 2 through 7. From days 8 through 14, both agents were applied twice daily 5 minutes apart.

Results: The maximum reduction of IOP (mean ± SEM) was 8.8 ± 1.9 mm Hg (26%) (P<.05) with latanoprost alone and 6.5 ± 1.0 mm Hg (21%) (P<.01) with 8-iso PGE<sub>2</sub> alone, 2 hours after the morning dosing on day 7. A further reduction of IOP of 4.0 ± 0.6 mm Hg was produced when 8-iso PGE<sub>2</sub> was added to latanoprost and of 3.0 ± 0.7 mm Hg was produced when latanoprost was added to 8-iso PGE<sub>2</sub> on day 13 before the morning dosing. Combination therapy with both agents caused maximum IOP reductions from baseline of 11.3 ± 3.0 mm Hg (33%) (P<.05) (latanoprost with 8-iso PGE<sub>2</sub> added) and of 9.8 ± 1.3 mm Hg (31%) (P<.01) (8-iso PGE<sub>2</sub> with latanoprost added) on day 14.

Conclusion: Latanoprost and 8-iso PGE<sub>2</sub> have an additive effect on IOP in glaucomatous monkey eyes.

Clinical Relevance: At least 50% of patients are treated with more than 1 ocular hypotensive medication. Thus, the determination of the additive effects on IOP of glaucoma medications will help to define optimum treatment regimens.

MATERIALS AND METHODS

Eight adult female cynomolgus monkeys (each weighing 3-5 kg), in which glaucoma had been induced unilaterally by repeated argon or diode laser photocoagulation of the midtrabecular meshwork, were used in this study.6

The IOP was measured hourly, beginning at 9:30 AM, for a total of 6 hours on day 1 (baseline day), days 6 and 7 (single-agent therapy), and days 13 and 14 (combination therapy) using a calibrated pneumotonometer (model 30 classic; Mentor Inc, Norwell, Mass). Five minutes before tonometry, 1 drop of 0.5% proparacaine hydrochloride was topically applied, and ketamine hydrochloride, 1 to 5 mg/kg, was administered intramuscularly for adequate sedation.

On each day of the study, 8-iso PGE₂ (Cayman Chemical Co Inc, Ann Arbor, Mich) was freshly prepared by dissolving in dimethyl sulfoxide, 100 g/L, and diluting with 0.9% sodium chloride to a 0.1% solution, a concentration that produces the greatest effect on IOP.4 The commercially available preparation of latanoprost, 0.005% (Pharmacia and Upjohn, Kalamazoo, Mich), was used, which is also at the top of the dose-response relation. On the drug treatment days, days 2 through 14, the first IOP measurement was taken just before the 9:30 AM dosing. On days 2 through 7, monkeys were treated twice daily with 1 drop of latanoprost, or with 0.1% 8-iso PGE₂, 25 µL, at 9:30 AM and 3:30 PM. On days 8 through 14, both 8-iso PGE₂ and latanoprost were applied twice daily at 9:30 AM and 3:30 PM, 5 minutes apart. The monkeys were treated unilaterally, in the glaucomatous eye only.

The following statistical analyses were performed using the 2-tailed paired t test: the change in IOP between baseline and single-agent therapy with latanoprost or 8-iso PGE₂, the change in IOP between single-agent therapy and combination therapy, the change in IOP with single-agent therapy on days 6 and 7, the change in IOP with combination therapy on days 13 and 14, and the change in IOP between combination therapy and baseline. A value of P<.05 was considered statistically significant. Data were calculated as the mean ± SEM. All experimental studies complied with the Association for Research in Vision and Ophthalmology Resolution on the Use of Animals in Research and were approved by the Mount Sinai School of Medicine, New York, NY, Institutional Animal Care and Utilization Committee.

maximum effect on IOP had been obtained by study day 6 for single-agent therapy and by study day 13 for combined therapy. Combination therapy resulted in additional IOP reductions at all measurement times on study day 13 compared with study day 6 and on study day 14 compared with study day 7. The average IOP on days 6 and 7 (single-agent therapy) was compared with the average IOP on days 13 and 14 (combination therapy) in each of the 2 treatment groups. The additional reductions in IOP were statistically significant (P<.05) at 0, 1, 3, and 6 hours when 8-iso PGE₂ was added to latanoprost, and from 0 through 4 hours when latanoprost was added to 8-iso PGE₂ (Figure). Additional

Effects of Single-Agent Therapy Followed by Combination Therapy on Intraocular Pressure in 4 Monkeys With Unilateral Glaucoma

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<tr>
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<th>Latanoprost + 8-iso Prostaglandin E₂</th>
<th>8-iso Prostaglandin E₂ + Latanoprost</th>
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<tr>
<td>Trough (0 h)</td>
<td>Baseline (day 1) 32.5 ± 1.9 33.3 ± 2.5</td>
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<td>First drug Day 6 28.3 ± 1.3 (13)§ Day 7 27.5 ± 1.9 (15)§ Both drugs Day 13 24.3 ± 1.3 (25)§ Day 14 24.0 ± 1.4 (26)§ Peak (2 h) Baseline (day 1) 33.8 ± 3.5 31.5 ± 2.0 First day 6 25.5 ± 2.5 (24)§ Day 7 25.0 ± 1.7 (26)§ Both drugs Day 13 22.0 ± 1.6 (35)§ Day 14 22.5 ± 0.9 (33)§</td>
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*Data are given as the mean ± SEM (percentage reduction from baseline) intraocular pressure, measured in millimeters of mercury. Single-agent therapy and combination therapy were given twice daily.
†Treatment was started with 0.005% latanoprost, and 0.1% 8-iso prostaglandin E₂ was added.
‡Treatment was started with 0.1% 8-iso prostaglandin E₂, and 0.005% latanoprost was added.
§Significant intraocular pressure reduction compared with baseline measurements (2-tailed paired t test, P < .05).
¶Significant intraocular pressure reduction for combination therapy compared with single-agent therapy (day 13 vs day 6 and day 14 vs day 7; 2-tailed paired t test, P < .05).

IOP reductions of up to 12% (3.8 ± 1.2 mm Hg) were noted when 8-iso PGE₂ was added to latanoprost and of up to 11% (3.6 ± 0.8 mm Hg) were noted when latanoprost was added to 8-iso PGE₂ 1 hour following morning dosing (Figure). Maximum reductions of IOP with combination therapy compared with baseline on day 14 were 11.3 ± 3.0 mm Hg (33%) (P < .05) when 8-iso PGE₂ was added to latanoprost and 9.8 ± 1.3 mm Hg (31%) (P < .01) when latanoprost was added to 8-iso PGE₂ (Table).

COMMENT

8-iso Prostaglandin E₂ is an isoprostane derivative. The isoprostanes are a unique series of prostaglandinlike compounds that have potential biological activity and take part in mediating the detrimental effects of oxidative stress in association with several human diseases. The biological effects of these compounds may be mediated through a unique isoprostane receptor.7 Latanoprost is not an isoprostane derivative. Thus, although latanoprost and 8-iso PGE₂ are prostaglandinlike compounds, they differ considerably.

Latanoprost reduces IOP by increasing non-pressure-dependent uveoscleral outflow.8 8-iso Prostaglandin E₂ reduces IOP by increasing traditional, tonographically measured, pressure-dependent outflow facility.9 Although both of these agents are prostaglandin derivatives, they reduce IOP through different mechanisms. The different effects of these 2 agents on IOP may be due to activity at different receptors, due to the fact that 8-iso PGE₂ is an isoprostane derivative and latanoprost is not, or due to other
as yet undetermined factors. The additivity of these 2 agents, for lowering IOP, as demonstrated in this study, is not unexpected. It occurs at concentrations that produce maximum effects on IOP. Clinical trials demonstrate that in some patients the effect of latanoprost is additive to cholinergic agents, which also reduce IOP by enhancing traditional tonographically measured outflow facility.

In the present study, latanoprost and 8-iso PGE$_2$, when applied as single agents, each reduced the IOP in glaucomatous monkey eyes. Peak IOP reductions were similar ($P<.30$) when comparing the effects of the 2 drugs, 26% after 6 days of dosing with latanoprost and 21% after 6 days of dosing with 8-iso PGE$_2$. Studies previously conducted in glaucomatous monkeys demonstrated comparable magnitudes of IOP reduction, up to 29% after 5 days of twice-daily dosing with latanoprost and up to 24% after 5 days of twice-daily dosing with 8-iso PGE$_2$. For either drug, reductions of IOP were similar on days 6 and 7, somewhat less than on day 5, suggesting that a longer duration of treatment would not produce an enhanced effect. In this monkey model, using latanoprost and 8-iso PGE$_2$ in combination resulted in additional IOP reductions of up to 12%. The small number of eyes in each treatment group, only 4, and the large fluctuations in IOP characteristically observed in the eyes of monkeys with laser-induced glaucoma explain why the additive effects on IOP that were observed at each point were not always statistically significant.

There has been considerable debate as to what is measured when using a tonographic technique. Tonographically measured outflow facility represents the sum of trabecular outflow facility, pseudofacility, and uveoscleral facility. Under normal circumstances, pseudofacility and uveoscleral facility in monkeys are each less than 0.02 µL/min per millimeter of mercury. Thus, it is most probable that increases in tonographically measured outflow facility following application of 8-iso PGE$_2$ to monkeys primarily represent an increase in trabecular outflow facility. The mechanism by which IOP was reduced with combination therapy with latanoprost and 8-iso PGE$_2$ was not measured in this study. The additive effect of the 2 drugs on IOP suggests that both uveoscleral outflow and traditional outflow facility are enhanced.

CONCLUSIONS

Prostaglandins are the newest class of compounds for managing glaucoma. Latanoprost or 8-iso PGE$_2$ when used alone lowers IOP less than when these agents are used in combination in glaucomatous monkey eyes. Tachyphylaxis does not occur. Thus, 8-iso PGE$_2$, a new prostaglandin compound that substantially differs from latanoprost, may have potential as a new agent for treating glaucoma.

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The colossal growth of all phases of ophthalmology during the last 20 years in both the clinical and the experimental field makes it impossible for the reader to keep abreast of the times without some process of condensation.