

A Comparative Study of Latanoprost (Xalatan) and Isopropyl Unoprostone (Rescula) in Normal and Glaucomatous Monkey Eyes

Janet B. Serle,* Steven M. Podos,* Yoshiaki Kitazawa,[†]
and Rong-Fang Wang*

Departments of Ophthalmology, *The Mount Sinai School of Medicine, New York, NY, USA;

[†]Gifu University School of Medicine, Gifu, Japan

Abstract: Latanoprost (PhXA41, Xalatan) and isopropyl unoprostone (UF-021, unoprostone, Rescula) two new prostanoid derivatives, have been shown to reduce intraocular pressure (IOP) significantly in patients with glaucoma or ocular hypertension. This study was designed to compare the ocular hypotensive effects of latanoprost and unoprostone in cynomolgus monkeys with glaucoma and characterizes the prostanoid's mechanisms of action in normal cynomolgus monkey eyes. Intraocular pressure was measured daily at 0, 0.5, and 1 hour and hourly for 5 additional hours during 1 baseline day, 1 vehicle-treated day, and 5 days of therapy with either 0.005% latanoprost or 0.12% unoprostone applied twice daily, at 9:30 AM and 3:30 PM, to the glaucomatous eye of eight monkeys with unilateral laser-induced glaucoma. Outflow facility was measured in six normal monkeys 3 hours prior to dosing and 1 hour after unilateral dosing with either drug. Aqueous humor flow rates were measured in six normal monkeys hourly for 4 hours on 1 baseline day and on 1 treatment day beginning 1 hour after administration of either drug to one eye. Intraocular pressure was significantly ($P < 0.005$) reduced after the first application for 4 hours with latanoprost and for 2 hours with unoprostone, up to 5.4 ± 0.8 mm Hg (mean \pm SEM) (latanoprost) and 3.8 ± 0.5 mm Hg (unoprostone). Intraocular pressure was significantly ($P < 0.005$) reduced for at least 18 hours following each PM dose of latanoprost. Intraocular pressure was not reduced ($P > .05$) 18 hours after each PM dose of unoprostone. An enhancement of the ocular hypotensive effect was observed from day 1 to day 5 with repeated dosing of either drug. Latanoprost produced a greater magnitude of IOP reduction for a longer duration of time than unoprostone after each application. Neither drug altered outflow facility or aqueous humor flow rates. Latanoprost and unoprostone appear to reduce IOP in monkeys by enhancing uveoscleral outflow. Latanoprost appears to be more efficacious and potent than unoprostone in reducing IOP in glaucomatous monkey eyes. **Jpn J Ophthalmol 1998;42:95-100** © 1998 Japanese Ophthalmological Society

Key Words: Aqueous flow, fluorophotometry, glaucoma, latanoprost, monkey, outflow facility, prostaglandin, unoprostone.

Introduction

Latanoprost (PhXA-41, Xalatan), a prostaglandin $F_{2\alpha}$ isopropyl ester derivative, markedly reduced intraocular pressure (IOP) in clinical trials of topical

administration of up to 1-year's duration.¹ Clinical investigations of latanoprost were carried out worldwide, and suggested once-daily administration of the drug has an ocular hypotensive efficacy similar to twice-daily administration of nonselective β -adrenergic antagonists.²⁻⁴ Side effects were few and of mild severity. Darkening of iris color was reported in up to 12% of patients.¹⁻⁴ Latanoprost 0.005% was approved by the United States Food and Drug Administration in June of 1996 for chronic administration in the management of glaucoma.

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Address correspondence and reprint requests to: Janet B. SERLE, MD, Mount Sinai Medical Center, Department of Ophthalmology, Box 1183, One Gustave L. Levy Place, New York, NY 10029

Isopropyl unoprostone (UF-021, unoprostone, Rescula), a prostaglandin metabolite-related compound, was extensively evaluated in laboratory^{5–7} and clinical trials in Japan.^{8–15} A clinical trial of 3-months' duration of topical administration suggested twice-daily administration of 0.12% unoprostone was similar in efficacy to twice-daily administration of 0.5% timolol.¹⁴ Few side effects of mild severity were reported for unoprostone. This drug was approved for clinical use in Japan.

The unique characteristic of prostaglandin derivatives that distinguishes some of them from the other classes of compounds given as drops to treat glaucoma is the mechanism by which they lower IOP. Prostaglandins enhance nontraditional, nonpressure-dependent, uveoscleral outflow. Direct measurement in laboratory animals using radioactive tracer techniques demonstrates marked increases in uveoscleral outflow following dosing with various F₂ prostaglandins.^{16,17} Indirect calculations of uveoscleral outflow show that latanoprost^{18,19} or unoprostone¹³ increase uveoscleral outflow in normal human volunteers. A direct comparison of the efficacy and the mechanism of reduction of IOP of latanoprost and unoprostone has not been performed.

In this study, glaucomatous monkeys were used to evaluate the comparative effects of unoprostone and latanoprost on IOP, and normal monkeys were used to evaluate the mechanism by which these drugs reduce IOP.

Materials and Methods

Eight adult female cynomolgus monkeys, (3–5 kg) with glaucoma-induced unilaterally by repeated argon laser trabeculoplasty,²⁰ were used to evaluate the effects of latanoprost and unoprostone on IOP. Intraocular pressure was measured with a pneumatonometer (Model 30 Classic, Mentor, Norwell, MA, USA) manometrically calibrated for the monkey eye. The monkeys were seated in specially designed chairs for IOP measurements. Prior to IOP measurements the monkeys were mildly sedated with ketamine hydrochloride (1–5 mg/kg intramuscularly) and a drop of 0.5% proparacaine hydrochloride (Alcaine, Alcon, Humacao, Puerto Rico) to each eye. On each day, IOP was measured at 9:30 AM, 10:00 AM, 10:30 AM, then hourly for 5 additional hours. For each set of experiments, the first day was the baseline day; vehicle and drugs were not instilled. The second day, monkeys were treated with one drop of vehicle at 9:30 AM and 3:30 PM to both eyes. On days 3 through 7, the monkeys were treated with either la-

tanoprost or unoprostone, one drop in the glaucomatous eye only, at 9:30 AM and 3:30 PM. There was a 2-week washout of the monkeys between the trials of the two drugs, during which they were not used for any other studies. Glaucomatous monkeys were used to evaluate the IOP effects of the two drugs because these animals have elevated IOP, which responds in a quantifiable manner to effective IOP-lowering drugs. Normal monkeys have very small IOP responses to IOP-lowering drugs, usually in the range of 1–2 mm Hg.

For each application of the drugs, latanoprost 0.005%, (Pharmacia & Upjohn, Kalamazoo, MI, USA), or unoprostone 0.12%, (Ueno Fine Chemicals Industry, Ltd. Osaka, Japan), or the vehicle 0.9% saline, were instilled using a single drop from a 50 μ L pipet.

Mechanism studies were performed in normal female cynomolgus monkeys with normal eyes, weighing between 3 and 5 kg. Outflow facility was measured using an electronic indentation tonograph (Alcon EDT-103, Fort Worth, TX, USA) on six monkeys anesthetized with intramuscular ketamine and topical proparacaine. The animals were placed in the supine position for tonographic measurements. Tonography was performed for 4 minutes on each eye, 3 hours prior to, and again 1 hour after, instilling each drug in one eye and vehicle in the contralateral eye. The animals were washed out for 2 weeks between the two drugs. Aqueous humor flow rates were determined on six monkeys using a scanning fluorophotometer (Coherent Fluorotron, Coherent, Palo Alto, CA, USA) and software analysis package.²¹ The animals were anesthetized with intramuscular ketamine and topical proparacaine prior to fluorescein iontophoresis. Fluorescein was iontophoresed into the central corneas of both eyes of each monkey for 7 minutes using 10% fluorescein in 2% agar gel, in the afternoon, 18 hours prior to each set of aqueous flow measurements. Aqueous humor flow rates were measured hourly for 4 hours beginning at 9:30 AM. On day 1, baseline flow rates were measured in both eyes without treatment. On day 2, each drug was applied unilaterally and vehicle was instilled into the contralateral eye at 8:30 AM and flow measurements were begun at 9:30 AM. Values of 102 μ L for anterior chamber volume and 40 μ L for corneal volume were used in the calculations of flow rates.²²

Results were analyzed for the drug-treated and vehicle-treated eyes using the paired *t*-test. Intraocular pressure effects of the two drugs were compared using the unpaired *t*-test. A value of *P* < 0.05 was considered statistically significant. All animal studies complied with institutional guidelines for animal ex-

perimentation and adhered to the ARVO resolution on the use of laboratory animals in research.

Results

Intraocular pressure reductions ($P < 0.01$) were observed on day 1 of treatment 60 minutes following the initial dose of latanoprost (Fig. 1) and 60 minutes following the initial dose of unoprostone (Fig. 2). The time of peak reduction of IOP for both of these drugs was 1 hour following dosing on each of the 5 treatment days (Fig. 3). Intraocular pressure was re-

duced ($P < 0.001$) on day 1 from 1 to 4 hours after the first dose of latanoprost compared to vehicle treatment. Latanoprost significantly ($P < 0.02$) reduced IOP at all measurements on days 2 through 5 compared to vehicle treatment. Intraocular pressure was reduced ($P < 0.005$) on day 1 at 1 and 2 hours after the first dose of unoprostone compared to vehicle

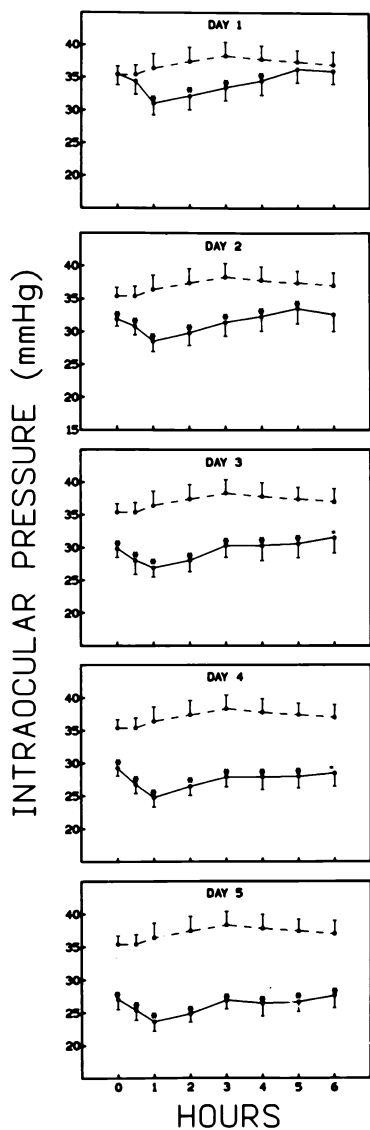


Figure 1. Effect on intraocular pressure (IOP) at 1 to 6 hours after morning dose of 0.005% latanoprost administered twice daily for 5 days to eight glaucomatous monkey eyes. *Statistically significant reductions in mean IOP \pm SEM compared to vehicle treatment ($P < 0.01$).

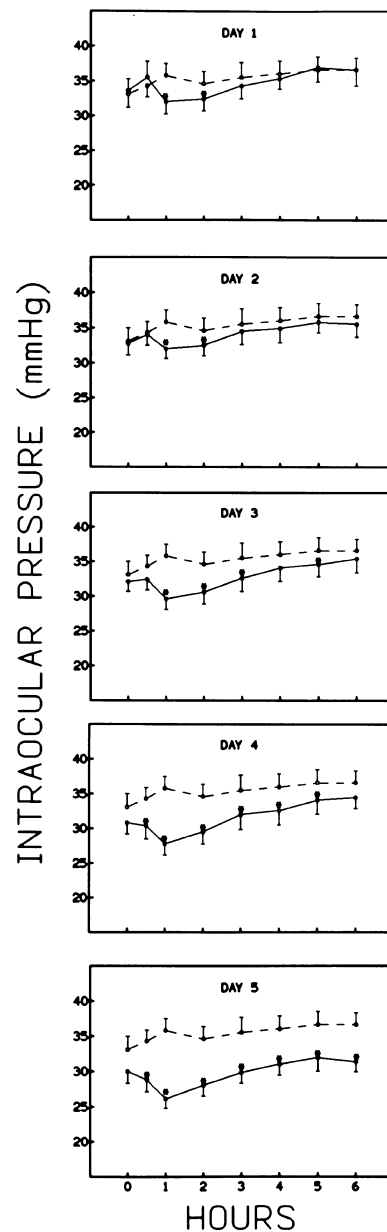


Figure 2. Effect on intraocular pressure (IOP) at 1 to 6 hours after morning dose of 0.12% unoprostone administered twice daily for 5 days to eight glaucomatous monkey eyes. *Statistically significant reductions in mean IOP \pm SEM compared to vehicle treatment ($P < 0.01$).

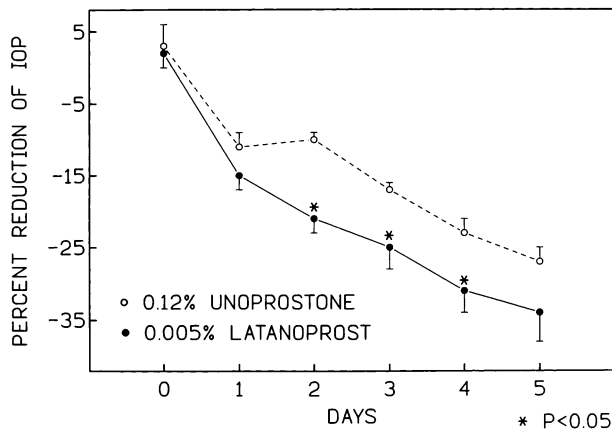


Figure 3. Comparison of the percent reduction of intraocular pressure (IOP) 1 hour after dosing with latanoprost or unoprostone, as compared to vehicle. *Statistically significant greater percent reduction of IOP with latanoprost than with unoprostone ($P < 0.05$).

treatment. Intraocular pressure was reduced ($P < 0.02$) on day 2 at 1 and 2 hours after AM dosing, on day 3 at 1, 2, 3, and 5 hours after AM dosing, and on days 4 and 5 at 0.5 through 6 hours after AM dosing with unoprostone compared to vehicle treatment.

The magnitude of IOP reduction was greater ($P < 0.05$) with latanoprost than with unoprostone at all measurement times on days 2 through 5, except 6 hours after dosing on days 2 and 3, and 1-hour post-dosing on day 5. Reduction of IOP was similar for the two drugs at these three times of measurements. On treatment days 2 through 5, IOP was reduced ($P < 0.005$) for at least 18 hours following the previous day's afternoon dose of latanoprost (Fig. 1). Eighteen hours following the previous day's afternoon dose of unoprostone, the lowering of IOP approached significance ($P > 0.05$) only on day 4 of treatment (Fig. 2). The duration of significant ($P < 0.05$) reductions of IOP following administration of unoprostone in-

Table 2. Effects of 0.005% Latanoprost or 0.12% Unoprostone on Aqueous Humor Flow Rates in Six Normal Monkeys

	Aqueous Humor Flow Mean \pm SEM (μ L/min)	
	Latanoprost	Unoprostone
Treated eyes	1.68 \pm 0.13	1.90 \pm 0.30
Baseline	1.86 \pm 0.20	1.97 \pm 0.16
Control eyes	2.11 \pm 0.19	1.91 \pm 0.25
Baseline	1.89 \pm 0.23	1.84 \pm 0.13

No significant change at 1 to 4 hours after administration of drug, as compared to baseline measurements.

creased from day 1 (hours 1 and 2) through day 5 (hours 0.5 through 6). The duration of reduction of IOP was maximum after the second dose of latanoprost, at least 18 hours. The magnitude of IOP reduction increased with both agents with repetitive dosing.

Mechanism studies demonstrated that facility of outflow was not altered ($P > 0.05$) 1 hour following application of latanoprost or unoprostone when compared to baseline measurements or contralateral vehicle-treated eyes (Table 1). Intraocular pressure was reduced ($P < 0.05$) in drug-treated eyes, compared to baseline measurements or contralateral vehicle-treated eyes, 1 hour following administration of latanoprost or unoprostone, just prior to performing tonography. Aqueous humor flow rates were unaltered ($P > 0.10$) in eyes receiving latanoprost or unoprostone compared to aqueous flow rates at baseline or in contralateral vehicle-treated eyes (Table 2).

Changes in iris color were not observed in any of the monkeys during this trial.

Discussion

This comparison of latanoprost and unoprostone, two prostaglandin analogues that have recently been

Table 1. Effects of 0.005% Latanoprost or 0.12% Unoprostone on Facility of Outflow in Six Normal Monkeys

	IOP Mean \pm SEM (mm Hg)		Outflow Facility Mean \pm SEM (μ L/min per mm Hg)	
	Latanoprost	Unoprostone	Latanoprost	Unoprostone
Treated eyes	13.2 \pm 0.7 ^a	13.0 \pm 1.0 ^a	0.76 \pm 0.08	0.65 \pm 0.05
Baseline	14.8 \pm 0.7	14.5 \pm 1.1	0.62 \pm 0.07	0.58 \pm 0.08
Control eyes	15.0 \pm 0.8	14.7 \pm 0.8	0.60 \pm 0.07	0.58 \pm 0.04
Baseline	15.7 \pm 0.3	15.3 \pm 0.9	0.73 \pm 0.08	0.53 \pm 0.05

^aSignificant reduction in IOP at 1 hour after unilateral drug administration compared with either baseline values or vehicle-treated eyes (two-tailed paired *t*-test, $P < 0.05$).

IOP: intraocular pressure.

made available for clinical use, demonstrated that either drug given twice a day effectively reduces IOP in monkey eyes made glaucomatous by repeat argon laser trabeculoplasty. Intraocular pressure was reduced 1 hour after the initial dose of either drug. Latanoprost had a longer duration of effect than unoprostone during the 5 treatment days. For the majority of measurements taken, reductions of IOP with latanoprost were of greater magnitude than with unoprostone. Peak reductions of IOP were up to 35% with latanoprost and up to 27% with unoprostone. Despite the 20-fold greater concentration of unoprostone than latanoprost, latanoprost appeared to be more efficacious in reducing IOP in the glaucomatous monkey eye. A single dose dose-response study performed in normal rhesus monkeys suggested unoprostone and PhXA34, the racemic mixture of latanoprost, had similar effects on IOP.²³ A clinical trial demonstrated that latanoprost is at least 1.5 times more effective than PhXA34 in reducing IOP in normal human subjects.²⁴

A similar comparison trial of latanoprost and unoprostone has not been reported in patients. A 2-week clinical trial demonstrated once-daily dosing with latanoprost was similar to twice-daily dosing with latanoprost.²⁵ Results from clinical trials suggest that 0.005% latanoprost administered once daily²⁻⁴ and 0.12% unoprostone administered twice daily¹⁴ are similar in efficacy to timolol administered twice daily. Differences in race of patients tested and frequency of administration in the aforementioned studies make it difficult to draw conclusions about the comparability of latanoprost and unoprostone in humans. Latanoprost appears to be more effective than unoprostone in monkeys. Conclusions pertaining to their comparability in humans await a controlled comparative study.

Studies of mechanism of action with various prostaglandin derivatives in monkeys and humans demonstrate that these agents reduce IOP by enhancing nonpressure-dependent uveoscleral outflow.^{13,16-19} Alterations in outflow facility and aqueous humor flow rates are usually minor and of insufficient magnitude to explain the observed reductions in IOP. This study confirms that the prostaglandins latanoprost and unoprostone do not alter outflow facility or aqueous humor flow rates in normal monkey eyes. Preliminary evaluations in rabbits indicate that both latanoprost and unoprostone⁷ increase uveoscleral outflow (unpublished observation Wang et al, 1996).

Xalatan and Rescula have greatly enhanced the options for the medical management of glaucoma. These drugs are extremely efficacious, producing re-

ductions of IOP that are similar in magnitude to nonselective β -adrenergic antagonists. The primary mechanism by which they reduce IOP is different than that of the commonly used treatments for glaucoma. The effect of latanoprost on IOP appears to be additive to that of β -adrenergic antagonists,^{26,27} cholinergic agents,²⁸ and orally administered carbonic anhydrase inhibitors.²⁹ Patients on maximum-tolerated medical therapy with uncontrolled IOP have further reductions in IOP following the addition of latanoprost (unpublished observations Gagliuso, Podos, and Serle, 1995) or unoprostone^{8,9} in nonrandomized trials, suggesting that these drugs are useful adjunctive therapy in patients on various other medications used to lower IOP.

Clinical trials have demonstrated that latanoprost and unoprostone are well tolerated. Darkening of iris color in patients with irides of certain colors, which has been observed with latanoprost²⁻⁴ has not been reported with unoprostone. Changes in iris color were not observed in any of the monkeys during this study. This is at least in part due to the short duration of the dosing (5 days). Randomized comparison trials in patients will help define similarities and differences in efficacy, safety, and tolerability of latanoprost and unoprostone, and whether one of these drugs may be advantageous in select patient populations.

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