Circadian Intraocular Pressure Management with Latanoprost: Diurnal and Nocturnal Intraocular Pressure Reduction and Increased Uveoscleral Outflow

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Abstract. Based on their mechanism of action, the most frequently used ocular hypertensive agents, the beta-blockers, cannot be assumed to reduce IOP during sleep. The need for drugs that reduce IOP around-the-clock is underscored, however, by the fact that inadequate nocturnal ocular perfusion pressure is considered to be one of the likely causes of glaucomatous optic neuropathy especially in some cases of normal tension glaucoma. The studies reviewed here demonstrate that latanoprost, a new ocular hypotensive prostaglandin $F_{2\alpha}$ analogue, applied once a day at a concentration of 0.005%, maintains a statistically highly significant IOP reduction around-the-clock. The magnitude of this IOP reduction was found to be essentially identical during the day and at night, both in patients maintained on timolol and in those not receiving other glaucoma medication. Latanoprost-induced IOP reduction was also found to be associated with increased uveoscleral outflow in normotensive volunteers, both during the day and at night. These circadian studies suggest that this new ocular hypotensive agent can be expected to be particularly useful for the medical management of some forms of glaucoma, such as normal tension glaucoma, when the cause of the glaucomatous damage cannot be linked specifically to diurnal IOP abnormalities. (**Surv Ophthalmol 41 [Suppl 2]:** S139–S144, 1997)

Key words. aqueous humor dynamics • circadian • diurnal • intraocular pressure • latanoprost • nocturnal • prostaglandins • timolol • uveoscleral outflow

In some cases of glaucoma, especially in so-called normal tension glaucoma, intraocular perfusion pressure can be particularly compromised during nocturnal episodes of systemic hypotension.[10,13] Nocturnal intraocular pressure (IOP) and blood pressure abnormalities may be the primary cause of the glaucomatous damage directly, or by increasing the chances of permanent foci of microvascular compromise following episodic ocular hypertension or IOP spikes.[3,4,13] In spite of this, the nocturnal hypotensive efficacy of glaucoma drugs have not been routinely evaluated, even after it was reported that timolol does not reduce IOP at night, and that beta-blockers do not reduce aqueous humor production during sleep.[8,20,21] In fact, timolol continues to be used even for the management of normotensive glaucoma, in spite of the fact that its cardiovascular side effects may compromise ocular perfusion pressure.[10,11]

Recently, a new group of ocular hypotensive agents, the prostaglandins (PGs), have been introduced and the $PGF_{2\alpha}$ derivative prodrug, latanoprost (previously known as PhXA41), has been found to provide effective IOP reduction as measured during the daytime, even when applied only once-a-day, either in the morning or in the evening, at a concentration of 0.005%,[1,9,24] Furthermore, latanoprost or its naturally-occurring parent compound, $PGF_{2\alpha}$ in its esterified prodrug form, was shown not to reduce aqueous humor production either during the day or at night,[7,26] and both animal and human studies show that PGs of the $F_{2\alpha}$ type, including latanoprost, reduce IOP primarily by increasing uveoscleral outflow.[2,7,17,22,23,26]

Recently published studies[6,16,19] have shown that once-daily latanoprost application yields an IOP reduction throughout the night that is comparable in extent to its daytime IOP reduction. A third study performed in Japan by the first three authors of this review (HKM, YK, MK and coworkers) has

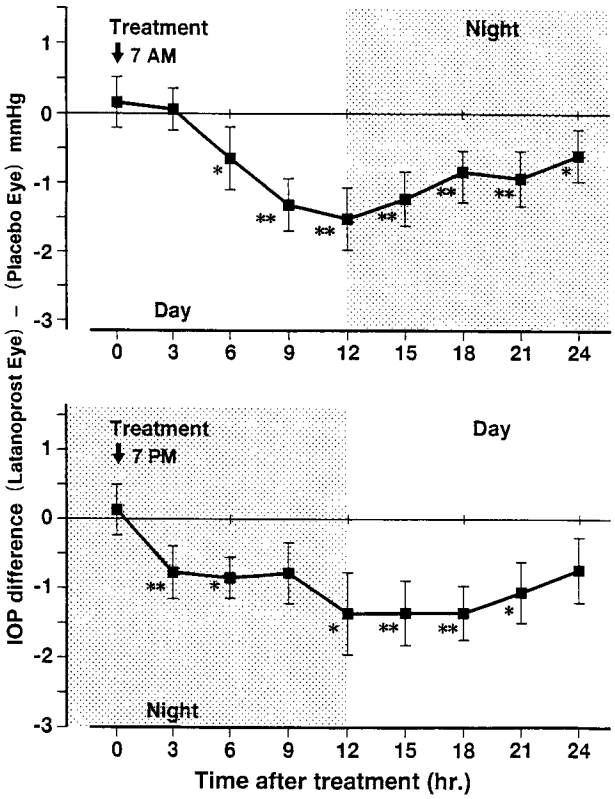

Fig. 1. The ocular hypotensive effect of a single dose of 0.005% latanoprost, when applied unilaterally at 7 AM (Panel A) or 7 PM (Panel B) to eyes of normotensive volunteers whose contralateral eyes were treated with a placebo solution at the same time. The asterisks indicate statistically significant IOP differences between the latanoprost- and placebo-treated eyes (*P < 0.05; **P < 0.001). The points represent means ± SEM, n = 16.

shown that this IOP reduction can be accounted for, both during the day and at night, by increasing uveoscleral outflow, without reducing the production of aqueous humor. These circadian IOP and aqueous humor dynamics studies will be reviewed here, briefly.

Circadian IOP Study on Normal Volunteers After a Single (Morning or Evening) Treatment with 0.005% Latanoprost

Sixteen healthy male volunteers (21–23 years of age) were recruited at the Hiroshima University School of Medicine.[16] For the first of two tests, eight subjects (Group 1) received one drop of latanoprost in one eye and its vehicle solution in the contralateral eye at 7 AM, while the other eight subjects (Group 2) received vehicle in both eyes. Three days later, Group 1 was treated bilaterally with placebo, and Group 2 received unilateral latanoprost (and contralateral placebo) treatment at 7 AM. Thereafter, the procedure was repeated, but the latanoprost and the placebo were administered at 7 PM.

IOP was measured directly before, and at 3-hour intervals for 24 hours after the administration of latanoprost or placebo, using a Goldmann applanation tonometer. The analyses reviewed here were based on comparing the IOP of the latanoprost-treated eye to the simultaneously measured IOP of the contralateral control eye of each subject.

Unilateral application of a single-dose of 0.005% latanoprost at either 7 AM (Fig. 1, Panel A) or at 7 PM (Fig. 1, Panel B) caused an IOP reduction in the latanoprost-treated eyes that was statistically significant at all time points indicated by asterisks in Fig. 1, as compared to the IOP of the contralateral placebo-treated eyes. The morning versus evening application of the drug had no apparent effect on the extent of IOP reduction in this small group of patients. In contrast, in a much larger long-term cross-over study,[1] the IOP reduction was found to be significantly greater following evening as compared to morning application of latanoprost. This circadian study clearly shows that a single dose of latanoprost decreases IOP in normotensive volunteers both during the day *and* throughout the night.

A Comparison of Nocturnal Versus Diurnal IOP Reduction in Ocular Hypertensive and Glaucoma Patients During the Course of Nine Days of Once Daily (Morning) Application of Latanoprost, with or without Concomitant Twice-Daily Treatment with Timolol

In contrast to the study conducted in Japan on normotensive volunteers, a study in Szombathely, Hungary, enlisted 17 glaucoma patients and two ocular hypertensives with IOPs >22 mm Hg, at the beginning of an up to four-week pre-enrollment period. These 19 patients (38–81 years of age) were divided into two groups. In group 2 (n = 10), all previous glaucoma medications were washed out, while patients in Group 1 (n = 9) continued on twice-daily timolol treatment.[19]

In the morning of Day 1 of the study period, patients were admitted to the hospital for baseline examinations and IOP measurements.[19] One drop of 0.005% latanoprost was then applied the next morning at 8 AM to one eye of each patient and placebo to the other eye by hospital staff in a randomized, double-masked protocol, using coded vials supplied by Pharmacia A.B. (Uppsala, Sweden). The patients left the hospital in the morning of the second day. On days 3–5, the patients came to the hospital, or were visited at their homes, and

to eliminate uncertainties about compliance with the application of the eye drops.

On the morning of Day 6, the patients were admitted again to the hospital. Their eyes were treated with latanoprost/placebo by hospital staff at 8 AM on that day and on the following four days (Days 7–10). In Group 1, timolol was also applied in the morning and evening by hospital staff. During these days of hospitalization, symptoms and ocular signs of possible side effects were registered as previously described[18] and IOP was measured at different times of the day and night, according to a schedule described in the original publication,[19] but not more than four times over any 24-hour period, and not more than once during each night, to minimize interference with normal sleep patterns.

In most cases, and always at night, IOP was first measured with a Tono-Pen XL electronic tonometer (Bio-Rad, Glendale, California) with the patient in the supine position, and in most cases also with a Goldmann applanation tonometer, followed by a second Tono-Pen reading, this time in the sitting position. On the 11th day, the last IOP measurements were taken at noon, 28 hours after the last treatment, and a closing examination was performed. The IOP of these patients was measured over this five-day period on 20 occasions, on most occasions with all three of the methods described above. Thus, both sitting and supine IOP values were accumulated over these five days of hospitalization to cover each two-hour period, representing a complete circadian cycle, with some duplicate time periods of measurements.

In both groups, the mean IOP values of the latanoprost-treated eyes were significantly reduced, but they essentially paralleled the mean IOP values of the placebo-treated contralateral eyes throughout the circadian cycle, regardless of whether the IOP was measured in the sitting or in the supine position.[19] This is illustrated in Fig. 2 for the IOP readings obtained with the Tono-Pen with the patients in the supine position, both during the day and at night. The supine Tono-Pen readings were taken at night with minimum disturbance, while the patient remained in bed.

The mean diurnal versus nocturnal latanoprost-induced IOP reduction (test eye versus placebo-treated eye) was –2.26 ± 0.30 versus –2.03 ± 0.33, and –3.19 ± 0.32 versus –3.26 ± 0.30 mm Hg as measured with the Tono-Pen in the supine position during the day and at night for Group 1 and Group 2, respectively. This <0.03 mm Hg difference between the diurnal and nocturnal mean IOP values, or these differences based on the Goldmann or

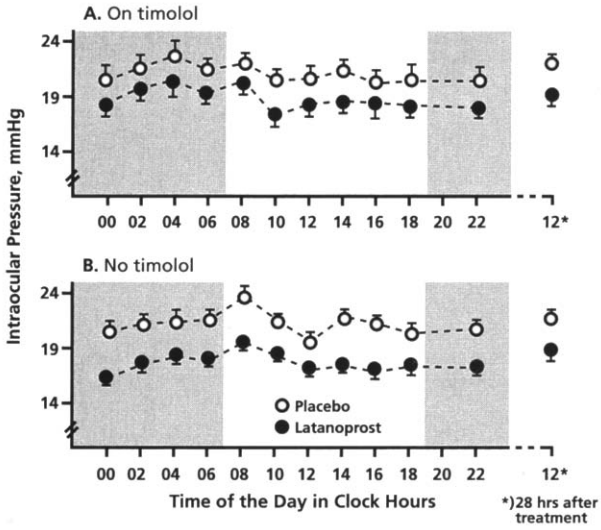

Fig. 2. The mean IOPs (±SEM) of ocular hypertensive or glaucomatous eyes collected between the fourth and ninth days of once-daily (8 AM) topical application of 0.005% latanoprost to one eye (solid circles) and its vehicle solution (placebo) to the contralateral control eye (open circle) of each patient. IOP values shown here were measured with a Tono-Pen XL applanation tonometer on patients in the supine position. In Panel A, the patients (n = 9) were maintained on twice-daily bilateral 0.5% timolol treatment, whereas patients shown in Panel B (n = 10) had all glaucoma medications washed-out before the beginning of nine days of latanoprost/placebo treatment. Shaded areas indicate measurements taken at night.

the same time points, were not statistically significant[19] ($P > 0.40$). Side effects were not noted and the local signs and symptoms observed or reported by the patient were not significantly different for the latanoprost- and placebo-treated eyes.[19]

The ocular hypotensive efficacy of latanoprost was also analyzed in terms of its ability to reduce the peak IOP value experienced by each patient. The highest IOP measurement of the control eye of each patient, obtained over the six-day in-hospital period, was compared to the corresponding IOP values measured at the same time in the latanoprost-treated test eyes. As shown in Table 1, the mean of the peak IOP values in the placebo-treated control eyes, both in Group 1 and Group 2, were significantly higher ($P < 0.03$ to $P < 0.0005$) than the mean of the corresponding IOP values of the contralateral latanoprost-treated test eyes. This reduction of IOP at the peak circadian IOP value of each patient was at least as much, or greater than the circadian IOP reduction shown in Fig. 2 here, or in the original publication for circadian IOP measurement taken in the sitting position.[19] Thus, the once-daily topical application of 0.005% latanoprost is

TABLE 1

The Means (± SEM) of the Peak Circadian IOP Values (mm Hg) of Each Control Eye During the Six-day Measurement Period, the Mean of the Corresponding IOP Value in the Contralateral Latanoprost-treated Test Eyes, and the Mean Percent IOP Difference Between the Latanoprost Treated Eyes and Contralateral Control Eyes at These Peak Values

	Tonopen				Goldmann	
	Supine		Sitting		Sitting	
	Group 1*	Group 2†	Group 1	Group 2	Group 1	Group 2
Mean of peak IOPs in control eyes	24.3 ± 1.0	25.3 ± 0.5	23.0 ± 1.2	24.0 ± 0.8	23.1 ± 1.3	24.4 ± 0.7
Mean of corresponding IOPs in test eyes	21.2 ± 1.4	20.4 ± 0.9	19.4 ± 1.4	19.4 ± 0.8	20.0 ± 1.1	19.3 ± 0.5
Percent of IOP reduction at peak	12.9 ± 4.5	19.2 ± 3.3	15.5 ± 4.8	18.5 ± 4.5	12.9 ± 3.8	20.3 ± 3.0
Significance‡ (P)	<0.03	<0.0005	<0.03	<0.005	<0.006	<0.0005

*Group 1, timolol + latanoprost vs. timolol + placebo (n = 9)
†Group 2, latanoprost only vs. placebo (n = 10)
‡P values, based on paired t-test of the IOP differences between test and control eyes

reducing the mean diurnal and nocturnal IOPs. The significance of this observation becomes clear if we consider the hypothesis, based on studies performed on other organ systems, that even relatively brief focal ischemic episodes, such as those caused by IOP spikes, may lead to the accumulation of small sites of permanent vascular damage in the optic nerve head.[3,4]

Diurnal and Nocturnal Latanoprost-induced Effects on Uveoscleral Outflow

A study was performed by the first three authors of this review (HKM, YK, and MT) on 13 normotensive (IOP <21 mm Hg) Japanese males of 21 to 23 years of age. The left eyes were treated with 30 µl of 0.005% latanoprost and the right eyes with placebo, five times over a three-day period, according to the treatment schedule shown in Table 2. This table also shows the schedule of oral carbonic anhydrase inhibitor (CAI), acetazolamide, and topical fluorescein administration, as well as the times of performance of measurements, required to calculate aqueous humor flow rate according to the Jones-Maurice method,[14] under two different rates of aqueous humor secretion, according to the method of Yablonski and coworkers.[12] The dimension of the cornea and the anterior chamber were estimated during the first day of the study with slit-lamp biomicroscopy.[15] Tonography was performed with a Müller tonometer over a four-minute period, while tonometry was performed with a Goldmann applanation tonometer at times shown in Table 2. The reported value[25] of 8 mm Hg was used for episcleral venous pressure in all calculations.

TABLE 2

Schedule of Measurements and Administrations

	Day 1	Day 2	Day 3
Latanoprost/placebo	8 AM, 8 PM	8 AM, 8 PM	8 AM
Oral acetazolamide	—	—	2 AM, 4 PM
Topical fluorescein	—	6 PM	6 AM
Fluorophotometry	—	—	12, 2, 4, 6 AM 12, 2, 4, 6 PM
Tonography	—	12 AM, 12 PM	—

The measured and calculated values of aqueous humor dynamics are presented in Table 3. There was no significant difference in aqueous humor flow between latanoprost- and placebo-treated eyes during the daytime, but a significantly ($P < 0.05$) greater aqueous humor flow was measured with fluorophotometry at night in the latanoprost-treated eyes, as compared to the contralateral placebo-treated eyes of these normotensive volunteers. As measured during the day, the IOP values were 13.1 ± 1.3 versus 10.5 ± 2.2 in the latanoprost-treated eyes and 15.1 ± 2.1 versus 12.9 ± 2.3 mm Hg in the control eyes for the pre-CAI versus post-CAI measurements, respectively. As measured during the night, these values were 12.5 ± 1.1 versus 11.6 ± 2.7 and 14.9 ± 2.0 versus 11.9 ± 2.3, respectively.

There was no significant difference between latanoprost-treated and control eyes in trabecular outflow facility, as measured during the daytime or at night (Table 3). In contrast, there was a significant increase in the calculated uveoscleral outflow

TABLE 3

*Calculated Parameters of Aqueous Humor Dynamics**

	Day Time			Night Time		
	PhXA41	Control	Difference	PhXA41	Control	Difference
Aqueous humor flow rate (μl/min)	2.23 ± 0.38	2.24 ± 0.25	ns	1.66 ± 0.05	1.44 ± 0.15	$p < 0.05$
Fluorophotometric Method:						
Outflow Facility (μl/min/mmHg)	0.22 ± 0.25	0.25 ± 0.03	ns	0.09 ± 0.04	0.09 ± 0.02	ns
Uveoscleral Outflow (μl/min)	1.19 ± 0.24	0.57 ± 0.07	$p < 0.05$	1.28 ± 0.16	0.78 ± 0.20	$p < 0.05$
Tonographic Method:						
Outflow Facility (μl/min/mmHg)	0.37 ± 0.03	0.28 ± 0.37	ns	0.37 ± 0.04	0.35 ± 0.03	ns
Uveoscleral Outflow (μl/min)	0.33 ± 0.4	−0.38 ± 0.56	$p < 0.05$	1.51 ± 0.12	1.23 ± 0.04	$p < 0.05$

*Mean ± S.E. (Day time: n = 7, Night time: n = 9) paired t-test
ns = not significant

contralateral placebo-treated eyes both during the daytime and at night. The extent of the apparent latanoprost-induced increase in uveoscleral outflow, measured by the fluorophotometric method during the daytime (Table 3), was comparable to the 0.87 ± 0.22 versus 0.14 ± 0.30 μl/min uveoscleral outflow, calculated for the latanoprost versus placebo-treated eyes using the same method in a previous study.[22,23] However, the study described here also shows that a comparable, statistically significant ($P < 0.05$) increase in uveoscleral outflow also occurs at night.

The uveoscleral outflow calculated from tonographic measurements yielded a smaller, albeit still statistically significant, difference between the latanoprost-treated and control eyes (Table 3). The interpretation of these tonographic values is made less reliable by the negative mean value obtained in the placebo-treated eyes during the daytime measurements, which may simply reflect random statistical variability in each of the measured parameters.

The fluorophotometric outflow facility measured at night was less than one half of that measured during the day, whereas the tonographic outflow facility was equal during the day and at night, higher in both cases than the daytime fluorophotometric outflow facility value. While we cannot rule out the possibility that this difference was simply due to errors in the measurements which were exaggerated by the calculations that are required to find the outflow facility by this fluorophotometric technique, it is possible that this reflects differences in outflow facility during sleep and during wakefulness. The fluorophotometric value represents the average flow rate between periods of sleep during the nighttime while the tonographic method is a direct determination of outflow facility obtained over four-minute periods at 12 noon and at midnight while the subjects were presumably awake, both during the daytime and at night. The observed decreased outflow facility during sleep is worthy of further investigation because of its implications regarding possible fundamental differences between diurnal and nocturnal patterns of aqueous humor dynamics, as it was discussed previously with respect to the required repair and maintenance of the canal of Schlemn.[3,5]

The fact that latanoprost reduces IOP by increasing uveoscleral outflow, both during the day and at night, is of great potential therapeutic significance with respect to the management of normal tension glaucoma (NTG). The nature of this outflow that reaches the zero pressure environment of the orbit[2] allows the IOP reduction to be very effective at low IOP values. As opposed to the effect of pilocarpine on outflow facility, for example, increased uveoscleral outflow allows the IOP to be reduced below the level of episcleral venous pressure, as it may be required in some cases of NTG.

Conclusion

These studies clearly demonstrated that once-daily topical application of 0.005% latanoprost provides significant around-the-clock IOP reduction, by increasing uveoscleral outflow, both during the daytime and at night. Once-daily latanoprost has been shown to be more effective, or at least as effective an ocular hypotensive agent as twice-daily timolol,[1] based on daytime IOP measurements, when timolol can also reduce IOP. The studies reviewed here suggest that latanoprost may be a particularly useful ocular hypotensive agent when the likely cause of the glaucomatous damage cannot be specifically associated with daytime events. The demonstrated nocturnal ocular hypotensive efficacy of latanoprost suggests that this new glaucoma drug can have particular therapeutic advantage over beta-blockers when the glaucomatous damage is associated with such nocturnal events as episodic systemic

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