The Effect of Latanoprost, Brimonidine, and a Fixed Combination of Timolol and Dorzolamide on Circadian Intraocular Pressure in Patients With Glaucoma or Ocular Hypertension

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Objective: To compare the circadian intraocular pressure (IOP) reductions induced by latanoprost, brimonidine tartrate, and a fixed combination of timolol maleate and dorzolamide hydrochloride in patients with primary open-angle glaucoma (POAG) or ocular hypertension (OHT).

Methods: In this crossover study, 10 patients with POAG and 10 with OHT were treated with latanoprost once a day, brimonidine twice a day, and a fixed combination of timolol and dorzolamide twice a day for 1 month. Four 24-hour tonometric curves were obtained for each patient. Intraocular pressure (IOP) was measured at 3, 6, and 9 AM, and at noon and at 3, 6, and 9 PM, and at midnight, using a handheld electronic tonometer with the patient in supine and sitting positions and a Goldmann applanation tonometer with the patient sitting at the slitlamp.

Main Outcome Measure: Reduction of circadian IOP.

Results: All the drugs significantly reduced IOP compared with the baseline at all times, except for brimonidine at midnight, 3 AM, and 6 AM. Latanoprost was more effective than brimonidine in lowering IOP at 3 and 6 AM and at 3 PM ($P=.03$), and the combination of timolol and dorzolamide was more effective than brimonidine at 3 and 9 AM ($P=.04$) and at 3 and 6 PM ($P=.05$) and more effective than latanoprost at 9 AM ($P=.05$).

Conclusion: Latanoprost and the fixed combination of timolol and dorzolamide led to similar circadian reductions in IOP, whereas brimonidine was less effective, particularly during the night.

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SEVERAL CURRENTLY available drugs reduce intraocular pressure (IOP) in patients with ocular hypertension (OHT) or primary open-angle glaucoma (POAG), but their efficacy is usually assessed on the basis of office measurements or, at best, diurnal IOP curves. Patients are rarely evaluated during the night,[1-14] even though this is a critical period for the control of glaucoma because of the possibility of a nocturnal decrease in systemic blood and optic nerve head perfusion pressure.[15-17] It has also been shown that both IOP and the rate of aqueous humor flow follow a circadian rhythm[18-26] and that IOP may be high immediately after awakening[20,27] because of local eyelid pressure from bedclothes during the night.[28] A recent study found that timolol maleate was less effective in reducing IOP during the night, whereas dorzolamide hydrochloride seemed to perform well from midnight to 9 AM.[4] Other studies have found that latanoprost reduces IOP to a similar extent during the night and day,[1-6,9,10,14] and the α_2-agonist brimonidine tartrate has been found to have a hypotensive effect, at least during the day, similar to that of a β-blocker.[29] It is hypothesized that a fixed combination of timolol and dorzolamide could provide 24-hour coverage as a result of the ocular hypotensive effect of timolol during the day and the good performance of dorzolamide during the night.[4,12]

The aim of this study was to compare the 24-hour effects of latanoprost, brimonidine, and a fixed combination of timolol and dorzolamide on the circadian rhythm of IOP in patients with POAG or OHT, a subject that has recently aroused some debate in the literature.[1-6,8-14]

METHODS

The method used to evaluate 24-hour IOP curves has been described in more detail elsewhere.[4] The present study included 20 patients with POAG or OHT. Glaucoma was defined as an untreated IOP of more than 21 mm Hg in at least 1 eye measured on 2 consecutive occasions separated by an interval of at least 2 hours but not more than 12 weeks, glaucomatous changes in the visual field or optic disc, or defects in the retinal nerve fiber layer.

Table 1. Patient Characteristics*

Characteristic	Patients (n = 20)
POAG	10
OHT	10
Age, mean (SD), y	63 (12.3)
Sex, male/female	9/11
IOP, mean (SD) at enrollment, mm Hg	23.5 (3.6)
Corneal thickness, mean (SD), mm	545 (30)
Prestudy therapy	
None	5
β-Blockers	10
Latanoprost	2
Combination†	3
Systemic hypertension	11
Treated with β-blockers	5
Other treatments	6

Abbreviations: IOP, intraocular pressure; OHT, ocular hypertension; POAG, primary open-angle glaucoma.
*Data are given as the number of patients, unless otherwise indicated.
†Combination of a β-blocker with pilocarpine (1 patient) or a β-blocker with dorzolamide (2 patients).

Ocular hypertension was defined as an untreated IOP of more than 21 mm Hg (measured as for glaucoma) with a normal visual field, optic disc, and retinal nerve fiber layer. All treated cases were controlled by medical therapy, and IOP levels during treatment were not considered as criteria for inclusion.

Exclusion criteria included a baseline untreated IOP of more than 30 mm Hg confirmed on 2 occasions within 1 week; angle-closure glaucoma; corneal abnormalities preventing reliable IOP measurement, including photorefractive keratectomy; previous filtration surgery; a life-threatening or debilitating disease limiting the patient's ability to participate in the trial; secondary causes of high IOP, such as the use of corticosteroids, iridocyclitis, or ocular trauma; conditions for which the trial drugs are contraindicated; having only 1 eye; or pregnancy. Significant wake-sleep rhythm disturbances and the regular use of hypnotic drugs as reported by the patients were also considered reasons for exclusion.

The trial had a crossover design, and patients already on medical treatment (all POAG cases and 5 OHT cases) underwent a 4-week washout period before their baseline circadian tonometric curves were recorded. The nature and purpose of the trial were explained in detail to all participants, who gave their informed consent before entering the washout phase. The study was carried out in accordance to the Declaration of Helsinki and was approved by the Ethical Committee of the University of Milan, Milan, Italy.

Using a list of random numbers, patients were randomized to receive 1 of the following treatment sequences: (1) A, B, C; (2) A, C, B; (3) B, A, C; (4) B, C, A; (5) C, A, B; or (6) C, B, A; where A=0.005% latanoprost (Xalatan; Pharmacia, Peapack, NJ), B=fixed combination of 0.5% timolol maleate and 2% dorzolamide hydrochloride (Cosopt; Merck, Whitehouse Station, NJ), and C=0.2% brimonidine tartrate (Alphagan; Allergan, Irvine, Calif). Participants were given masked bottles and instructed to instill the eyedrops according to the study protocol, once daily for drug A (9 PM) and twice daily for drugs B and C (8 AM and 8 PM). Each trial drug was administered for 1 month, after which a circadian tonometric curve was recorded. Patients were washed out for about 4 weeks between each regimen of medications. A total of 4 circadian tonometric curves were therefore obtained for each patient, 1 baseline and 3 different treatment curves.

Patients entered the hospital at 8 AM and stayed for 24 hours. During the periods of hospitalization, patients were allowed to follow a regular lifestyle, including reading, watching television, and playing cards, and received normal hospital meals without any beverage restrictions, including small amounts of beer or wine and coffee or tea. No measurements were taken during known periods of increased or decreased consumption of drinks that could potentially alter IOP. Patients were also given an ad hoc questionnaire designed to assess their reaction to hospitalization, anxiety due to measurements, quality of sleep, etc. The waking period lasted from approximately 6:30 AM to 11 PM. A complete ophthalmological examination (including corneal pachymetry) was performed, and any information about systemic and local drug tolerability was recorded. Intraocular pressure was measured at 3, 6, and 9 AM, at noon, at 3, 6, and 9 PM, and at midnight. During hospitalization, drugs were administered by study personnel according to the protocol: latanoprost at 9 PM, just before the tonometric reading, and the twice-daily drugs 1 hour before the IOP evaluation. In the case of the daytime measurements (9 AM to 9 PM), patients were asked to go to bed and relax for about 15 minutes, after which supine IOP was measured in both eyes. Subsequently, their blood pressure was measured, and they were then asked to sit on the bed for further ocular pressure measurements. The interval between the supine and sitting IOP measurements did not exceed 5 minutes. After walking approximately 10 meters, patients reached the nearest examination room, where a third IOP value was measured at the slitlamp. During the night (midnight to 6 AM), patients were awakened about 10 minutes before their IOP and blood pressure were measured following the same procedure. The IOP measurements were made using a handheld electronic tonometer (TonoPen XL; Bio-Rad Laboratories, Hercules, Calif) with the patient in supine and sitting positions and a Goldmann applanation tonometer with the patient sitting at the slitlamp. All measurements were taken by 2 well-trained evaluators (A.B. and P.F.), who were masked to the treatment assignment, and tested for measurement consistency and agreement before starting the study ($\kappa=0.82$); κ values were calculated for a ± 2 mm Hg difference and for the supine position evaluation.

The study outcome was the difference in IOP values between the groups. If both eyes were eligible, only 1 (chosen at random) was used for analytical purposes.

The sample size was calculated assuming that a difference in mean IOP of 2.5 mm Hg was clinically relevant. With $\alpha=.05$, $1-\beta=0.90$, and an SD of 2 mm Hg, approximately 20 patients were needed. Between-group differences were tested for significance by means of parametric analysis of variance, and the Bonferroni method was used to adjust *P* values. All analyses were performed using SPSS statistical software, version 6.0 (SPSS Inc, Chicago, Ill), for Macintosh.

RESULTS

The main characteristics of the 20 patients (10 with POAG and 10 with OHT) are shown in **Table 1**. All patients completed the 3 crossover phases, and no important adverse events were recorded. **Figure 1** shows Goldmann tonometer IOP values measured at baseline and after each treatment period. All the drugs significantly reduced IOP in comparison with the baseline at all points, except for brimonidine at midnight, 3 AM, and 6 AM. The mean (SD) IOP values were 22.6 (2.7) mm Hg at baseline, 16.7 (0.6) mm Hg after latanoprost, 16.9 (1.4) mm Hg after the combination of timolol and dorzolamide, and 18.7 (1.9) mm Hg after brimonidine. The differences in mean IOP values were statistically significant between latanoprost and brimonidine ($P=.005$) and between the combination of timolol and dorzolamide and brimonidine ($P=.01$). There was

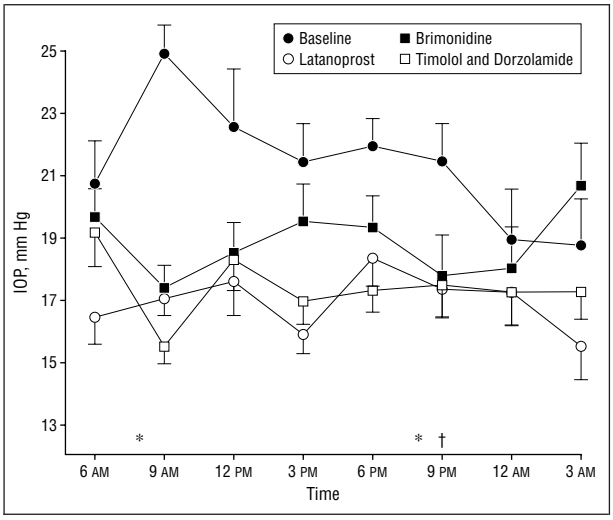

Figure 1. Goldmann tonometer intraocular pressure (IOP) readings (mean [SD]). All drugs significantly reduced IOP in comparison with the baseline except for brimonidine tartrate at midnight, 3 AM, and 6 AM. Latanoprost was more effective than brimonidine at 3 and 6 AM and at 3 and 6 PM (P=.03). The fixed combination of timolol maleate and dorzolamide hydrochloride was more effective than brimonidine at 3 and 9 AM (P=.04) and at 3 and 6 PM (P=.05). It was also more effective than latanoprost at 9 AM (P=.05). Asterisks indicate the times when brimonidine and the fixed combination of timolol and dorzolamide were administered; dagger, the time when latanoprost was administered.

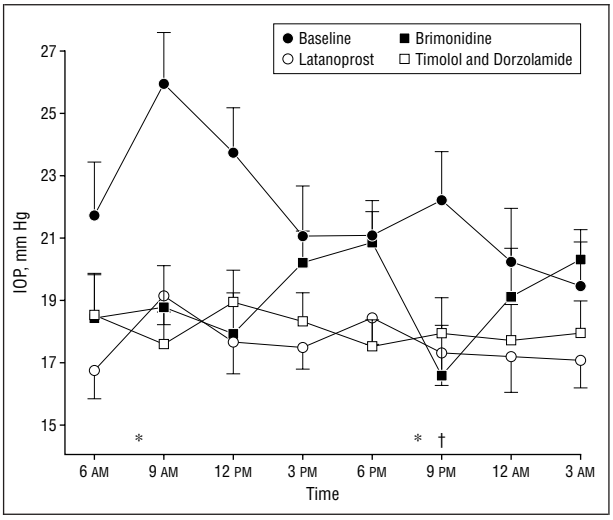

Figure 2. Supine position tonometric readings (mean [SD]). All drugs significantly reduced intraocular pressure (IOP) in comparison with the baseline except for brimonidine tartrate at midnight, 3 AM, 3 PM, and 6 PM. Latanoprost was more effective than brimonidine at midnight, 3 AM (P=.02), and 6 AM (P=.04) and at 3 and 6 PM (P=.03). Latanoprost was more effective than the fixed combination of timolol maleate and dorzolamide hydrochloride at 6 AM (P=.05), which was more effective than brimonidine at 3 AM (P=.05), 3 PM, and 6 PM and more effective than latanoprost at 9 AM (P=.05). Asterisks indicate the times when brimonidine and the fixed combination of timolol and dorzolamide were administered; dagger, the time when latanoprost was administered.

Table 2. Change in Intraocular Pressure (IOP)*

	Mean (%) Change From Baseline, mm Hg		
Time	Latanoprost	Timolol Maleate and Dorzolamide Hydrochloride	Brimonidine Tartrate
6 AM	−4.2 (20.3)	−2.1 (10.0)	−1.2 (5.8)
9 AM	−7.7 (30.8)	−9.5 (38.0)	−7.3 (29.2)
12 PM	−4.6 (20.7)	−4.0 (18.0)	−3.8 (17.1)
3 PM	−5.4 (25.3)	−4.2 (19.7)	−1.6 (7.5)
6 PM	−3.7 (16.9)	−4.5 (20.5)	−2.6 (11.9)
9 PM	−4.1 (19.1)	−3.9 (18.2)	−3.6 (16.8)
12 AM	−1.7 (9.0)	−1.7 (9.0)	−1.0 (5.2)
3 AM	−3.0 (16.0)	−2.0 (10.6)	0.9 (4.7)

*Goldmann tonometer IOP readings.

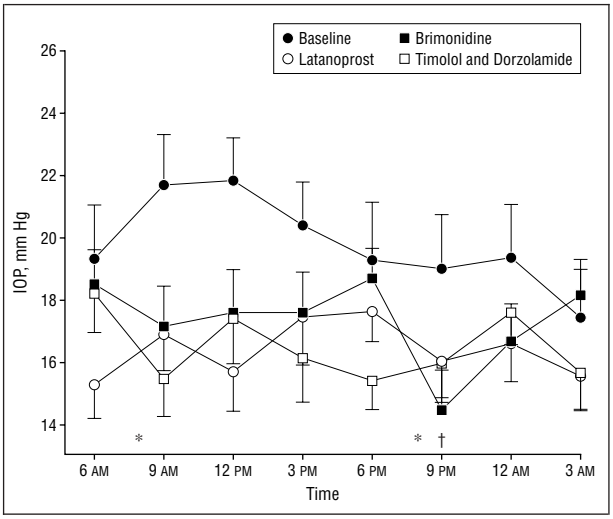

Figure 3. Sitting position tonometric readings (mean [SD]). All drugs significantly reduced intraocular pressure (IOP) in comparison with the baseline except for brimonidine tartrate at 3 AM, 6 AM, and 6 PM. Latanoprost was more effective than brimonidine at 3 and 6 AM (P=.02) and at noon (P=.03). It was more effective than the fixed combination of timolol maleate and dorzolamide hydrochloride at 6 AM (P=.01), which was more effective than brimonidine at 3 AM (P=.04), 9 AM (P=.05), and 6 PM (P=.01) and more effective than latanoprost at 6 PM (P=.03). Asterisks indicate the times when brimonidine and the fixed combination of timolol and dorzolamide were administered; dagger, the time when latanoprost was administered.

no statistically significant difference in the mean IOP values between the latanoprost group and the combination of timolol and dorzolamide group.

Latanoprost was more effective in lowering IOP than was brimonidine at 3 AM, 6 AM, and 3 PM (P=.03). The fixed combination of timolol and dorzolamide was more effective than brimonidine at 3 and 9 AM (P=.04) and at 3 and 6 PM (P=.05). It was also more effective than latanoprost at 9 AM (P=.05). In comparison with the baseline, mean (SD) diurnal (9 AM to 9 PM) vs nocturnal (midnight to 6 AM) reductions in IOP were −5.8 (1.2) mm Hg vs −4.1 (0.8) mm Hg for latanoprost (P=.09), −6.1 (2.2) mm Hg vs −3.2 (1.5) mm Hg for the fixed combination (P=.03), and −4.4 (1.8) mm Hg vs −0.8 (1.0) mm Hg for brimonidine (P=.01). **Table 2** shows the change in IOP from baseline for each study drug.

Figure 2 and **Figure 3** show supine and sitting electronic tonometer measurements; the shape of the curves was consistent with those obtained using the Goldmann tonometer, and the differences in drug efficacy were similar. The statistical significance of between-drug comparisons is also shown. As was previously reported,[4] Goldmann tonometer readings agreed well with electronic tonometer readings in the sitting position (r=0.8), whereas electronic tonometer values measured with patients in a

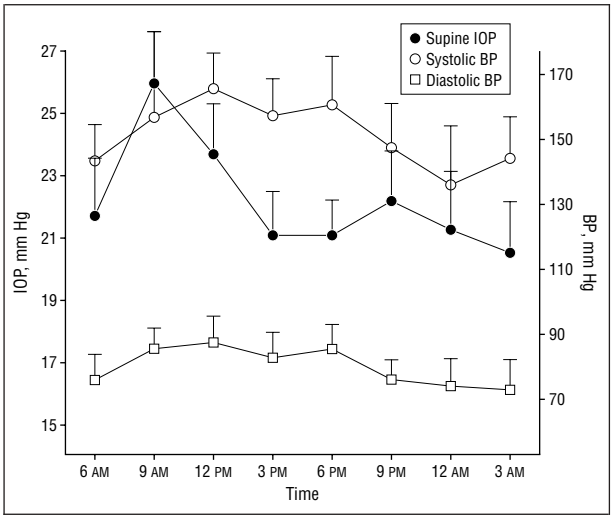

Figure 4. Baseline (mean [SD]) supine position tonometric intraocular pressure (IOP) and blood pressure (BP) readings in patients with primary open-angle glaucoma or ocular hypertension. No nocturnal IOP peak in correspondence with a nocturnal BP dip was observed.

supine position were higher. The mean (SD) supine vs sitting IOP values were 23.2 (1.9) mm Hg vs 22.3 (1.7) mm Hg at baseline, 17.6 (1.1) mm Hg vs 16.6 (1.0) mm Hg after latanoprost, 17.8 (1.8) mm Hg vs 16.7 (1.4) mm Hg after the combination of timolol and dorzolamide, and 19.3 (2.1) mm Hg vs 18.5 (1.9) mm Hg after brimonidine.

Blood pressure measurements and the corresponding supine IOP values at baseline are shown in **Figure 4**.

Responses to the questionnaire indicated that the overall quality of the days and nights spent in the hospital for the measurements of circadian IOP was "normal."

COMMENT

The results of this trial suggest that the effects of the 3 treatments may vary considerably during different phases of the circadian IOP curve. All drugs led to a statistically significant decrease in IOP in comparison with the baseline, except for brimonidine during the night. As was reported in previous studies,[1-6,9,10,14] the effect of latanoprost administered once daily in the evening appeared to be fairly uniform throughout the circadian cycle but was slightly, although not significantly, greater during the day.[4,5] This finding can be explained by the fact that latanoprost is most effective 12 to 18 hours after administration.[5,9] In addition, in a recent trial, the efficacy of the fixed combination of latanoprost and timolol administered at 8 AM was found not to be significantly different from that of placebo at 3 AM,[6] when the baseline IOP measurement was lowest. A further explanation might involve the ability of prostaglandins to relax nocturnal ciliary muscle tone and thus increase uveoscleral outflow.[2,30] The fixed combination of timolol and dorzolamide was effective in reducing IOP at 9 AM, and its effect was superior to that induced by latanoprost. The combination was significantly more effective during the day than during the night, and the difference reached statistical significance. This finding might be explained by the fact that timolol loses some of its effect during the night.[31-35] Several studies indicate that the rate of aqueous flow during sleep is much lower than during waking hours[31-33,36,37] and that drugs affecting aqueous flow can have different effects at different times of day.[31,33,38,39] Timolol, which substantially decreases aqueous flow during the day, has been found to have no measurable effect at night[33-35] because of the existence of a baseline flow rate that cannot be further suppressed by any drug or the lack of timolol-blockable activity in the sleeping eye.[31,40,41] On the contrary, it has been found that dorzolamide retains its good hypotensive action during the night,[4,12] a finding confirmed by our own results. When interpreting the magnitude of the response to the combination, the fact that 5 patients (25% of the sample) were already taking systemic β-blockers should be considered. The difference between the diurnal and nocturnal effects of brimonidine was statistically significant. Brimonidine is a selective α_2-agonist that has been found to have a daytime hypotensive effect similar to that of timolol,[29,42-44] and we also found that its mean daytime effect on IOP was good in comparison with the baseline (–4.4 mm Hg; 25%). The marked decrease in efficacy during the night observed in this trial may have been due to the frequency of administration; it has been found that brimonidine is more effective in controlling diurnal IOP when administered 3 times rather than twice daily, which induces a marked and long-lasting trough period.[44] However, brimonidine is currently given twice daily in clinical practice. To the best of our knowledge, relatively few studies have evaluated the nocturnal efficacy of brimonidine. In a recent trial, Konstas et al[44] found that brimonidine was more effective in reducing the 24-hour IOP when given 3 times daily rather than twice daily, except for the morning measurements. On the other hand, the lack of effect of brimonidine during the night cannot be supported by studies of aqueous humor flow, indicating that α-agonists (unlike timolol) can suppress the aqueous flow at night.[45]

Finally, it must be noted that the administration time for latanoprost (9 PM) was different than the times for twice-daily dosing (8 AM and 8 PM), and consequently IOP measurements were at different times after administration.

The supine and sitting circadian curves recorded on the basis of the handheld electric tonometer and the Goldmann measurements were basically similar, but, as expected, sitting values were lower than the tonometric supine values because of the increase in venous pressure in the supine position. However, the postural effect on IOP was less than may have been expected, probably because we adopted a short interval between the supine and sitting measurements to limit as much as possible the measurement-related awakening time during the "sleeping period."

This study was designed to detect a 2.5–mm Hg difference between treatment arms. We are aware that there may be situations in which smaller differences would be helpful, although for studies such as this one a big and clinically relevant difference in treatment effect will be much more straightforward to interpret.

Any trial such as ours is naturally exposed to a series of biases that cannot be easily avoided and must be taken into consideration when interpreting the results. The most important biases concern the measurement of IOP in a clinical setting: hospitalization, sudden awakenings and exposure to light for nocturnal measurements, and disturbed sleeping patterns may all affect the evaluation of

IOP. We tried to limit these biases as much as possible by using a randomized crossover design that assured their even distribution across all treatment periods. Furthermore, a special questionnaire was used to assess the "normality" of the time spent in the hospital. Finally, it should be mentioned that, although drug bottles were masked, patients might have distinguished latanoprost from the other 2 drugs on the basis of the frequency of dosing. Evaluators, on the other hand, were masked to treatment assignment and frequency of administration.

Despite these potential limitations, the results of this trial once again suggest the importance of assessing nocturnal IOP because considerable variations in pressure were recorded that would not have been revealed by diurnal curves or isolated office-hour measurements. It has recently been pointed out that fluctuations in IOP seem to be an important risk factor for the progression of glaucoma,[46] so efforts to detect them should be made in order to prevent the worsening of the disease. It has been widely demonstrated that, at least in some patients, different OHT drugs can have different effects on IOP during a 24-hour period, and 24-hour IOP recordings might help ensure the complete evaluation of OHT drug regimens, particularly in those patients experiencing progression of the disease. In fact, nocturnal IOP evaluation could reveal abnormal spikes that would be overlooked if only diurnal measurements are considered.

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