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

Nicola Orzalesi, MD; Luca Rossetti, MD; Andrea Bottoli, MD; Elena Fumagalli, MD; Paolo Fogagnolo, MD

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.


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, 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. It has also been shown that both IOP and the rate of aqueous humor flow follow a circadian rhythm, and that IOP may be high immediately after awakening because of local eyelid pressure from bedclothes during the night. 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. Other studies have found that latanoprost reduces IOP to a similar extent during the night and day, and the β2-agonist brimonidine tartrate has been found to have a hypotensive effect, at least during the day, similar to that of a β-blocker. 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.

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.

METHODS

The method used to evaluate 24-hour IOP curves has been described in more detail elsewhere. 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.
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 trial 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). Patients were asked to go to bed and relax for about 15 minutes, after which supine IOP was measured in both eyes. The patients 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 application 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 (κ=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 α=0.05, 1–β=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
The fixed combination of timolol maleate and dorzolamide hydrochloride was more effective than brimonidine at 3 and 6 AM 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.

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 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.

Table 2. Change in Intraocular Pressure (IOP)*

<table>
<thead>
<tr>
<th>Time</th>
<th>Latanoprost</th>
<th>Timolol Maleate and Dorzolamide Hydrochloride</th>
<th>Brimonidine Tartrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 AM</td>
<td>−4.2 (20.3)</td>
<td>−2.1 (10.0)</td>
<td>−1.2 (5.8)</td>
</tr>
<tr>
<td>9 AM</td>
<td>−7.7 (30.8)</td>
<td>−9.5 (38.0)</td>
<td>−7.3 (29.2)</td>
</tr>
<tr>
<td>12 PM</td>
<td>−4.6 (20.7)</td>
<td>−4.0 (18.0)</td>
<td>−3.8 (17.1)</td>
</tr>
<tr>
<td>3 PM</td>
<td>−5.4 (25.3)</td>
<td>−4.2 (19.7)</td>
<td>−1.6 (7.5)</td>
</tr>
<tr>
<td>6 PM</td>
<td>−3.7 (16.9)</td>
<td>−4.5 (20.5)</td>
<td>−2.6 (11.9)</td>
</tr>
<tr>
<td>9 PM</td>
<td>−4.1 (19.1)</td>
<td>−3.9 (18.2)</td>
<td>−3.6 (16.8)</td>
</tr>
<tr>
<td>3 AM</td>
<td>−1.7 (9.0)</td>
<td>−1.7 (9.0)</td>
<td>−1.0 (5.2)</td>
</tr>
<tr>
<td>6 AM</td>
<td>−3.0 (16.0)</td>
<td>−2.0 (10.6)</td>
<td>0.9 (4.7)</td>
</tr>
</tbody>
</table>

*Goldmann tonometer IOP readings.

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 −3.8 (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, 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
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, 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. This finding can be explained by the fact that latanoprost is most effective 12 to 18 hours after administration.

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.

The 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**

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
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