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 application 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.

Circadian tonometric curves were therefore obtained for each patient. Fifty-one patients were enrolled in the study. Patients were washed out for about 4 weeks before their IOP and blood pressure were measured following the ophthalmological examination (including corneal pachymetry) and the twice-daily drugs 1 hour before the 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 3 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 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 pressure curve was recorded. The nature and purpose of the trial were explained in detail to all participants, who gave informed consent before starting the study.

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 tonometric 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 no important adverse event.
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 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>12 AM</td>
<td>−1.7 (9.0)</td>
<td>−1.7 (9.0)</td>
<td>−1.0 (5.2)</td>
</tr>
<tr>
<td>3 AM</td>
<td>−3.0 (16.0)</td>
<td>−2.0 (10.6)</td>
<td>0.9 (4.7)</td>
</tr>
</tbody>
</table>

*Asterisks indicate the times when brimonidine and the fixed combination of timolol and dorzolamide were administered; dagger, the time when latanoprost was administered.

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 midnight, 3 AM, 6 PM, and 6 AM. Latanoprost was more effective than brimonidine at 3 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 = .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.

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 midnight, 3 AM, 6 PM, and 6 AM. Latanoprost was more effective than brimonidine at 3 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 = .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.
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.”

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. 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, 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. 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 differences reached statistical significance. This finding might be explained by the fact that timolol loses some of its effect during the night. Several studies indicate that the rate of aqueous flow during sleep is much lower than during waking hours and that drugs affecting aqueous flow can have different effects at different times of day. Timolol, which substantially decreases aqueous flow during the day, has been found to have no measurable effect at night 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. On the contrary, it has been found that dorzolamide retains its good hypotensive action during the night, 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 α2-agonist that has been found to have a daytime hypotensive effect similar to that of timolol, 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. 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 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. 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, so efforts 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.

Submitted for publication January 24, 2002; final revision received October 24, 2002; accepted December 26, 2002.

Corresponding author and reprint requests: Nicola Orzalesi, MD, Institute of Biomedical Sciences, University of Milan, San Paolo Hospital, Via di Rudini, 820142 Milan, Italy (e-mail: lucamrossetti@libero.it).

REFERENCES


5. Larsson LJ. Intraocular pressure over 24 hours at repeated administration of latanoprost 0.005% or timolol gel-forming solution 0.5% in patients with ocular hypertension. Ophthalmol. 2001;108:1439-1444.

6. Larsson LJ. Effect of intraocular pressure during 24 hours after repeated administration of the fixed combination of latanoprost 0.005% and timolol 0.5% in patients with ocular hypertension. J Glaucoma. 2001;10:109-114.


11. Konstas AG, Mantziris DA, Maltezos A, Cate EA, Stewart WC. Comparison of 24-hour control with timolopic 0.5% and timolopic-XE 0.5% in patients with primary open-angle glaucoma. Acta Ophthalmol Scand. 1999;77:S41-543.