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.

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 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 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 (k=0.82); k 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=.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

#### Table 1. Patient Characteristics

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

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).
timolol and dorzolamide were administered; dagger, the time when latanoprost was administered.

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

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.

**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 AM</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>

*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,3 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. 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. 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 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.”

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 Goldman measurements were basically similar, but, as expected, supine 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

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.
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