Comparative study of the pressure lowering efficacy and variations in the ocular pulse amplitude between fixed combinations of dorzolamide/timolol and brinzolamide/timolol

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Objective: To determine possible differences in the intraocular pressure (IOP) and ocular pulse amplitude (OPA) lowering capacity of the fixed drug combinations of dorzolamide/timolol and brinzolamide/timolol.

Methods: In this cross-sectional study, one of the eyes of 25 healthy subjects was randomly assigned to treatment with dorzolamide/timolol and the other eye with brinzolamide/timolol. After instilling the drops, possible adverse effects (e.g., blurred vision, itching) were assessed in each eye. This assessment was repeated 30 min later. IOP and OPA were determined in each eye by dynamic contour tonometry at baseline and 2 h following treatment.

Results: Both fixed drug combinations significantly reduced IOP and OPA with no differences detected between treatment groups. Among the adverse effects recorded, itching was significantly greater in the first assessment in the eyes treated with dorzolamide/timolol (p = 0.011). This difference was no longer apparent in the second assessment.

Conclusions: Both fixed combinations were similarly effective in reducing intraocular pressure and ocular pulse amplitude. Adverse effects related to both treatments were mild and well tolerated, though itching occurred most frequently in the eyes treated with dorzolamide/timolol.

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Estudio comparativo de la eficacia hipotensora y de las variaciones en la amplitud de pulso ocular entre las combinaciones fijas dorzolamida/timolol y brinzolamida/timolol

Resumen

Objetivo: Evaluar las diferencias en cuanto a eficacia hipotensora y amplitud de pulso ocular entre las combinaciones fijas de dorzolamida/timolol y brinzolamida/timolol.

Métodos: Estudio transversal en 25 sujetos sanos. En cada paciente uno de los ojos fue tratado con la combinación fija dorzolamida/timolol y el otro con brinzolamida/timolol. La asignación fue realizada al azar en cada paciente. Tras la instilación, mediante una escala visual analógica se evaluaron los posibles efectos adversos (visión borrosa, picor...). Las diferencias se evaluaron con un análisis paramétrico.

Resultados: Ambas combinaciones disminuyeron de forma significativa la presión intraocular y la amplitud de pulso ocular en ambos grupos. Las diferencias fueron en ambos casos leves y bien tolerados presentándose únicamente el picor como más frecuente en los ojos tratados con dorzolamida/timolol.

Conclusiones: Ambas combinaciones demostraron ser igualmente eficaces, produciendo variaciones similares y significativas en la amplitud de pulso ocular. Los efectos adversos fueron en ambos casos leves y bien tolerados presentándose únicamente el picor como más frecuente en los ojos tratados con dorzolamida/timolol.

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Introduction

Glaucoma is a chronic optic neuropathy that evolves with progressive loss of the retina ganglion cell axons. The main risk factor for the development and progression of this disease is the increase of intraocular pressure (IOP). However, numerous and recent studies have evidenced the role played by ocular perfusion alterations and loss of self-regulation in the pathogenesis of glaucoma. Vascular risk factors include vasospastic events which damage its self-regulation and hemodynamic changes that reduce the perfusion pressure (no pressure, organic changes in vessel walls, etc.).

The purpose of this paper is to assess differences in what concerns hypotensive efficacy and ocular pulse amplitude (OPA) between fixed combinations of dorzolamide/timolol and brinzolamide/timolol.

Subjects, materials and methods

A transversal study was carried out on 25 healthy subjects consecutively recruited in the Glaucoma Dept. of the San Carlos Clinical Hospital of Madrid, Spain. One of the eyes of each subject was treated with a fixed combination of dorzolamide/timolol (Merck Sharp & Dohme Laboratories, France) and the other with brinzolamide/timolol (Alcon Laboratories, UK). The allocation was random in each patient so that they would not know which drug was being administered to each eye (simple blind). The protocol study was approved by the ethical committee of the hospital and all the patients signed the informed consent in accordance with the Helsinki declaration.

After the administration, possible adverse effects were assessed with an analog visual scale (blurred vision, itch, tearing and stinging) in each eye. This assessment was repeated 30 min after the administration. Utilizing a dynamic contour tonometer or Pascal tonometer (TCD, SMT Swiss Microtechnology AG, Port, Switzerland), the data recorded were IOP and ocular pulse amplitude (OPA) at the time of the administration and 2 h later.

The dynamic contour tonometer or Pascal tonometer was equipped with a concave 7 mm diameter terminal which adapts to the contour of the cornea and allowed it to maintain its shape and curvature, exhibiting the minimum distortion and without requiring applanation for measuring IOP. A digital pressure sensor included in the concave surface of the tonometer directly measured the transcorneal IOP. An LCD display shows the intraocular pressure in mmHg after each measurement, within a range of 5–200 mmHg as well as the reliability of the measurement (Q) and the ocular pulse amplitude, i.e., the intraocular pressure difference between systole and diastole, which indirectly indicates the ocular blood flow. The measurements with good reliability (Q ≥ 3) were recorded for each eye, discarding low reliability measurements and repeating them immediately to obtain the mean value for subsequent analysis.

For all subjects, the mean arterial pressure (MAP) was obtained by means of the formula MAP = diastolic pressure + 1/3 (systolic pressure – diastolic pressure), and the heart frequency (HF) at the time of administration and 2 h later with an automatic digital sphygmomanometer (Omron, HEM-742).

Finally, the subjects were asked to state their subjective overall preference between the 2 eyedrops. The statistical analysis was carried out with an ANOVA test and a t for
In contrast, in our study we analyzed the retrobulbar hemodynamic variation being statistically significant (in the first assessment. However, this difference disappeared significantly greater in the eyes treated with dorzolamide/timolol no statistically significant differences were found (paring the IOP reduction between both fixed combinations, statistically significant manner (between both fixed combinations (cant differences were found when comparing the reduced IOP with the fixed combination of dorzolamide/timolol was at baseline to 63.6 ± 17 at the end of the study, with p = 0.086. As regards to the overall subjective preference of the administered eyedrops, 68% of the subjects chose the brinzolamide/timolol fixed combination and 24% chose dorzolamide/timolol; 8% of the patients expressed no preferences.

Discussion

Recently, the role played by anti-glaucomatous drugs on the ocular blood flow has been studied, particularly the function of carbonic anhydrase inhibitors. Under normal conditions, carbonic anhydrase catalyzes the hydration of CO₂ and its transformation into carbonic acid which is subsequently released in the form of H⁺ and HCO₃⁻. Accordingly, carbonic anhydrase inhibitors increase the local concentration of CO₂ and therefore generate acidosis which leads to lessen dilatation and increased local blood flow. The hypotensive effect of carbonic anhydrase inhibitors is derived from their action on the ciliary body, diminishing the production of aqueous humor. In our study we have observed a significant reduction of OPA together with an improvement of ocular blood flow in both treatment groups, albeit without significant differences between them. In a similar manner, Martínez and Sánchez-Salorio analyzed the retrobulbar hemodynamic parameters by means of Doppler and IOP in patients with progressive open angle glaucoma who were administered dorzolamide or brinzolamide added to timolol 0.5%. After 5 years of follow-up, they observed a significant reduction of IOP and an increase of ocular perfusion pressure in both groups, even though the improvement of the retrobulbar blood flow parameters was obtained only in the patients who were administrated dorzolamide. In a subsequent study, they observed how the fixed combination of dorzolamide/timolol diminished for the same reason the risk of progression compared to the other treatments. In contrast, in our study we assessed healthy subjects and made an indirect measurement

**Table 1 – Adverse effects 5 min after administering both eyedrops.**

<table>
<thead>
<tr>
<th>Side effects</th>
<th>D/T</th>
<th>B/T</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blurred vision</td>
<td>2.25 ± 2.7</td>
<td>1.8 ± 2.3</td>
<td>0.53</td>
</tr>
<tr>
<td>Itching</td>
<td>2.6 ± 2.7</td>
<td>1.5 ± 1.5</td>
<td>0.011</td>
</tr>
<tr>
<td>Stinging</td>
<td>4.1 ± 3.0</td>
<td>2.7 ± 2.1</td>
<td>0.085</td>
</tr>
<tr>
<td>Tearing</td>
<td>2.1 ± 2.3</td>
<td>2.3 ± 2.5</td>
<td>0.744</td>
</tr>
</tbody>
</table>

Itching was the only statistically significant adverse effect (p = 0.011) although it disappeared in the second assessment 30 min after administration. In the second assessment (30 min later) (Table 1). MAP was of 94.1 ± 0.1 at baseline, going down to 87.8 ± 9.9 2 h after administering the eyedrops, with p = 0.008. HF varied from 74.7 ± 13.3 baseline to 63.6 ± 17 at the end of the study, with p = 0.086. As regards to the overall subjective preference of the administered eyedrops, 68% of the subjects chose the brinzolamide/timolol fixed combination and 24% chose dorzolamide/timolol; 8% of the patients expressed no preferences.

**Fig. 1 – IOP reduction 2 h after treatment. Significant IOP reduction with dorzolamide/timolol (p = 0.009) and brinzolamide/timolol (p = 0.001) fixed combinations. No significant differences between both treatment groups (p = 0.824).**

Student test for paired data with the SPSS version 15.0 (SPSS Inc., Chicago, IL, USA) statistical software. A value of p ≤ 0.05 was taken as statistically significant.
Fig. 2 – OPA 2 h after treatment. Significant reduction of OPA with dorzolamide/timolol (p = 0.043) and with brinzolamide/timolol (p = 0.011) fixed combinations, without significant differences between both treatment groups (p = 0.916).  

Conflict of interests  
None of the authors have declared any conflict of interests.  

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