Hypotensive effects of dorzolamide eyewash in maximal therapy glaucoma patients: A comparative study with oral acetazolamide

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Introduction

Carbonic anhydrase inhibitors (CAI) have been an integral part of anti-glaucomatous therapy for over 40 years. Their hypotensive action depends on their capacity of inhibiting aqueous humour production with no significant effect on its outflow. But their use in glaucoma therapy is greatly limited by the high frequency of adverse reactions. Amongst the drugs that have been tried, dorzolamide is the one that has been found to have the highest hypotensive efficacy, both in experimental animals and man. The recent marketing of this drug for topical use has opened up the possibility of supplanting systemic CAIs with topical ones.

The aim of our work was to compare ocular hypotensive efficacy of a dose of dorzolamide eyewash with that of acetazolamide tablets in healthy volunteers and in glaucomatous patients in a regime of maximal therapy.

Patients and methods

All the participants in the study signed informed consent declarations before joining. Admitted patients were aged between 52 and 85 years. The mean age of the patients was 69.6±7.1 years, with a range from 59 to 81 years, for 10 women and 12 men. The mean age of the control group was 71.4±5.8 years for 4 women and 6 men, while, in the other group, the mean age was 67.5±8.06 years for 6 women and 6 men. The first group, the controls, was composed of patients who had come to our Institute for cataract extraction. The second group was formed of patients with diagnosed chronic simple open-angle glaucoma receiving the maximum tolerated medical therapy (beta-blockers b.i.d., adrenergics b.i.d., pilocarpine t.i.d.). Exclusion criteria included systemic treatment that could affect intraocular pressure (IOP), other ocular therapies not in the study, prior ocular surgery, signs of recent ocular inflammation, and hypersensitivity to the drugs in the study.

Study design

A crossed, masked study was set up. The two groups had three pressure curves taken at intervals of at least 7 days. The first curve was taken in basic conditions for both groups, The subsequent two curves were taken respectively, after administration of one acetazolamide 250 mg tablet and after instillation of one drop of dorzolamide 2% eyewash. The measurements were made every 2 hours, starting from 9 a.m., until the end of the treatment's hypotensive effect. The first was made immediately before the treatment.

Statistical analysis

Statistical analysis of the results was made in the worse eye, i.e. the eye with the higher pressure at the first measurement of the curve without treatment, or, if the value was the same in both eyes, choice fell on the right eye.

The statistical analysis was carried out on the 22 patients who completed the protocol. The main efficacy parameter evaluated was IOP modification of the base curve at the same hour.

The statistical evaluation was accomplished with the Mann-Whitney non-parametric U-test, considering a value of p=0.05 significant, with the use of the programme Systat 5.2 for McIntosh (Tolentino, USA).

Results

The results showed a statistically significant reduction of the OP in the non-glaucomatous control group after treatment with acetazolamide at 2 hours (p=0.00018) and a 4 hours (p=0.0010), while pressure diminution was no longer significant at 6 hours. The dorzolamide-treated control group had a statistically significant IOP reduction at 2 hours (p=0.0008) and at 4 hours (p=0.008), though at 6 hours it was no longer statistically significant. There was no statistically significant difference in hypotensive effect between the two treatments at any time of the study. In the glaucomatous patients in therapy, acetazolamide addition to the on-going medical therapy caused a statistically significant IOP reduction at 2 hours

Table 1.

Mean ± s.d. and percentage diminution of OP after therapy in the healthy controls.

Examination times and hours after therapy	no therapy	Acetazolamide	Dorzolamide 2%
9 a.m. (0)	16.6 ± 3.1	15.8 ± 3.2	16.0 ± 2.5
11 a.m. (2)	17.07 ± 3.3	12.1 ± 1.5 (23.4%)	13.0 ± 1.6 (18.7%)
1 p.m. (4)	16.40 ± 2.5	13.4 ± 2.5 (15.1%)	13.7 ± 1.9 (14.3%)
3 p.m. (6)	16.30 ± 2.9	14.9 ± 2.4 (5.9%)	15.6 ± 2.3 (2.5%)

Mean ± s.d. and percentage diminution of OP after therapy in glaucomatous patients

Examination times and hours after therapy	Massive therapy	Acetazolamide	Dorzolamide 2%
9 a.m. (0)	18.1 ± 3.2	19.1 ± 4.1	20.0 ± 3.5
11 a.m. (2)	18.8 ± 2.6	15.5 ± 3.0 (18.8%)	15.1 ± 2.0 (24.5%)
1 p.m. (4)	18.5 ± 3.0	16.6 ± 2.7 (13.0%)	15.2 ± 1.6 (24.0%)
3 p.m. (6)	17.5 ± 2.9	17.1 ± 1.7 (10.4%)	16.7 ± 2.1 (16.5%)

(p=0.01) and at 4 hours (p=0.005) after administration of the tablet, while at 6 hours the decrease was no longer statistically significant.

Instillation of dorzolamide 2% eyewash in glaucomatous patients produced a statistically significant decrease at 2 hours (p=0.006) and 4 hours (p=0.006), but no statistically significant difference at 6 hours after treatment (Table 1).

Comparison of the two additional therapies in the glaucomatous patients showed a greater hypotensive effect by dorzolamide 2% eyewash at 4 hours after treatment, but without statistically significant differences. The mean age of the patients was 69.6±7.1 years, with a range from 59 to 81 years, for 10 women and 12 men. The mean age of the control group was 71.4±5.8 years for 4 women and 6 men, while, in the other group, the mean age was 67.5±8.06 years for 6 women and 6 men.

Discussion

Our study has demonstrated that dorzolamide eyewash has an ocular hypotensive efficacy superposable on that of acetazolamide tablets and that administration of either systemic or topical CAIs produced an acute IOP reduction both in the controls and in the glaucomatous patients receiving massive medical therapy. The hypotensive efficacy of both drugs proved superposable both in the controls and in the glaucomatous patients, which would suggest, therefore, the expedience of using dorzolamide 2% eyewash instead of systemic CAI therapy in patients already receiving maximum topical medical therapy.

It remains, possibly, to establish whether the contemporaneous use of systemic and topical CAIs might lead to further tonometric decrease.

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2% dorzolamide and cornea: An ultrabiomicroscopic study

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Purpose

Dorzolamide is a water soluble, specific, topical inhibitor of human carbonic anhydrase (CA) isoenzyme CA II, which is the predominant CA isoenzyme in the ciliary process. Inhibition of CA II involves a reduction of aqueous humour production. This isoenzyme is found also in the corneal endothelium and in other ocular structures such as lens, Muller cells, retinal pigment epithelium and parafoveal cones (1). So far, the long-term effect of dorzolamide on the corneal endothelium has not been established. In this study we investigated the effect of 2% dorzolamide eye drops (2% Trusopt®, MSD) on the cornea of glaucomatous patients.

Methods

We used an ultrabiomicroscopic technique to measure the central corneal thickness in 30 eyes of 20 patients (12 m, 8 f, mean age: 61.4±4 years), with primary open angle glaucoma (POAG) treated with 2% dorzolamide t.i.d. (treated group) and in 10 untreated fellow eyes (control group). To avoid bias owing to pressure-related corneal changes, we enrolled patients previously treated with 0.5% betaxolol b.i.d. and excluded eyes undergoing changes in IOP ≥ 3 mmHg after 30 days of treatment with 2% dorzolamide t.i.d. Other exclusion criteria were the presence of corneal anomaly and/or previous ocular surgery. After informed consent, we measured corneal thickness before changing therapy (t0) and after 3 (t3) and 6 (t6) months of therapy with 2% dorzolamide t.i.d. for the treated group, while maintaining the untreated eyes as a control group (also measured at baseline (t0) and after 3 (t3) and 6 (t6) months). We used Humphrey UBM System 840 (Humphrey-Zeiss, San Leandro, Ca.) for corneal thickness measurements. By generating a videofrequency A-scan vector on the B-scan frozen image, corneal peak-to-peak measurements become highly accurate and reproducible. The matched pairs t-test was used to test for significant changes from t0 values in central corneal thickness. We also evaluated visual acuity and endothelial cell count.

Results

So far as the treated group was concerned, mean central corneal thickness at baseline (t0) was 0.510±0.033 mm, at t3 it was 0.528±0.042 mm and at t6 it was 0.527±0.048 mm. Mean change from baseline (t0) was +0.018 mm (3.53 %, p< 0.01) at t3, +0.017 mm (3.33%, p<0.01) at t6, while change between t3 and t6 was -0.001mm (0.18%, p=n.s.). As for the control group, mean central corneal thickness at baseline (t0) was 0.515 ±0.032 mm, at t3 it was 0.512±0.035 mm and at t6 it was 0.516±0.028 mm. Mean change from baseline (t0) was -0.003 mm (0.58%, p=n.s.) at t3, +0.001 mm (0.19%, p=n.s.) at t6, while change between t3 and t6 was +0.004 mm (0.78%, p=n.s.). Visual acuity and endothelial cell count showed no significant changes from baseline at any time.