INITIAL CLINICAL EXPERIENCE WITH BRINZOLAMIDE 1% OPTHALMIC SUSPENSION (AZOPT®)

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SUMMARY – The aim of the study was to assess the intraocular hypotensive effect of 1.0% brinzolamide (b.i.d.) as monotherapy in patients with primary and secondary glaucoma. The six-month study included 20 patients of which 19 completed the study (one patient was excluded due to allergic drug reaction). All patients had previously received local antiglaucoma therapy. Because of local undesired side effects and inadequate control of intraocular pressure they were switched to treatment with 1.0% brinzolamide as monotherapy. Intraocular pressure was measured on the day of therapy introduction, and then at 15 days, one month, three months and six months of therapy. Nineteen patients successfully completed the six-month study. A clinically significant decrease in the intraocular pressure was recorded. The difference in intraocular pressure between the baseline (23.8 ± 2.4), and 15-day (18.2 ± 2.8), one-month (18.2 ± 2.7), three-month (18.5 ± 2.9) and six-month (18.8 ± 3.2) levels was statistically significant (p<0.001). Deviation from the mean values of intraocular pressure was considered as standard deviation. Local side effects such as scratching and pricking were recorded in three patients, however, there were no systemic or other side effects. Results of the study suggested monotherapy with 1.0% brinzolamide (b.i.d.) to be successful in the regulation of intraocular pressure in patients with primary or secondary glaucoma.

Key words: Carbonic anhydrase inhibitors, therapeutic use; Carbonic anhydrase inhibitors, adverse effects; Glaucoma, drug therapy

Introduction

Brinzolamide belongs to a new class of heterocyclic sulfonamide carbonic anhydrase inhibitors (CAIs) that are topicaly active in reducing intraocular pressure (IOP). It has a high affinity and inhibitory potency against human CA II, an isozyme of carbonic anhydrase found in the ciliary epithelium, which are involved in aqueous humor secretion. Brinzolamide is formulated as an aqueous humor suspension at a physiologic pH. The optimum concentration of brinzolamide for lowering elevated IOP is 1.0%, based on dose-response studies over the concentration range from 0.3% to 3.0% when administered twice daily (b.i.d.)

The 1.0% brinzolamide ophthalmic suspension is well tolerated and does not produce many of the side effects associated with CAIs when administered systematically, making it an attractive treatment for patients with glaucoma in whom compliance with therapy may pose a problem. It reduces IOP from baseline in a statistically significant and clinically relevant manner in the majority of patients when used as either primary or adjunctive therapy. The primary objective of this study was to evaluate dual therapy (alpha-blocking agents, beta-blocking agents), the IOP lowering efficacy of 1.0% brinzolamide (b.i.d.) as monotherapy upon replacing current therapy (alpha-blocking agents and beta-blocking agents latanoprost) for different types of glaucoma, to investigate the existence of subjective side effects, and to examine systemic or other adverse effects over a period from baseline to six months of therapy.
Patients and Methods

The patients treated at the University Department of Ophthalmology, Sestre milosrdnice University Hospital in Zagreb were considered for inclusion in the study. The study was performed during a six-month period. Upon obtaining approval from the appropriate regulatory authorities and ethics committees, oral consent was obtained from all patients before participation in the study.

Table 1. Types of glaucoma in 36 eyes of patients who completed the study

<table>
<thead>
<tr>
<th>Type of glaucoma</th>
<th>f</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary open angle glaucoma (POAG)</td>
<td>24</td>
<td>66.7</td>
</tr>
<tr>
<td>Post pars plana vitrectomy</td>
<td>2</td>
<td>5.6</td>
</tr>
<tr>
<td>Thyrotoxic orbitopathy</td>
<td>4</td>
<td>11.1</td>
</tr>
<tr>
<td>Pseudoexfoliation glaucoma</td>
<td>6</td>
<td>16.7</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Primary glaucoma: 24 (66.7%) Secondary glaucoma: 12 (33.3%)

The criteria for the use of brinzolamide in glaucoma patients were as follows: 1) inadequate current antiglaucoma therapy with IOP higher than 21 mm Hg (17 patients), and 2) poor drug tolerance (three patients). Twenty patients (12 women and eight men) were selected, with 19 patients aged 58 ± 7 years having completed the study. One male patient had to be excluded from the study for allergic reaction to brinzolamide. A majority of patients (n=12) had primary open angle glaucoma (POAG), i.e. 24 eyes were involved. Secondary glaucoma was less common, i.e. in three patients with pseudoexfoliation glaucoma (6 eyes), two patients with thyrotoxic orbitopathy (4 eyes), and two patients after pars plana vitrectomy (PPV) (2 eyes). Thus, a total of 36 eyes were included in the study (Table 1).

Brinzolamide replaced previous therapy with beta-blocking agents, alpha-blocking agents, latanoprost and a combination of beta-blocking agent and latanoprost. Clinical examination included case history, determination of visual acuity, computerized visual field assessment, measurement of IOP according to Goldmann’s applanation tonometry, biomicroscopy, gonioscopy and ocular fundus examination by direct ophthalmoscopy.

Determination of visual acuity, visual field testing by standard full-threshold automated static perimetry (dG2 program on an Octopus Visual Field analyzer) and ophthalmoscopy were performed at the beginning and at the end of the study. Gonioscopy was performed at the beginning of the study to confirm the diagnosis of glaucoma. Biomicroscopic examination was performed daily in order to determine the occurrence of local side effects. IOP was measured by Goldmann applanation tonometry. Two measurements were performed in each eye and the mean of two measurements was used on statistical analysis. IOP was recorded at baseline, and then at 15 days, one month, three months and six months of the introduction of brinzolamide. Examinations were performed at 9.00 a.m. and 1.00 p.m.

Statistical analysis

Results are presented as values of descriptive statistics, i.e. mean and standard deviation, median, and minimal and maximal value. Differences in values during the study period were tested by Friedman’s test. As differences in the values during the study period were statistically significant, the differences between every two given measurements and differences between the initial and each following measurement were tested by Wilcoxon’s test. Differences between the measured values in the groups of primary and secondary glaucoma were tested by Mann-Whitney U test. Statistical analyses were done by use of the SPSS software (SPSS for Windows 10.0, SPSS Inc., Chicago, IL, USA).

Table 2. Differences in IOP values during the study period

<table>
<thead>
<tr>
<th>Time point</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
<th>z*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>23.8</td>
<td>±2.4</td>
<td>23.8</td>
<td>18.0</td>
<td>32.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 days</td>
<td>18.2</td>
<td>±2.8</td>
<td>18.0</td>
<td>14.0</td>
<td>24.0</td>
<td>-5.238*</td>
<td>0.000</td>
</tr>
<tr>
<td>1 month</td>
<td>18.2</td>
<td>±2.7</td>
<td>18.0</td>
<td>13.5</td>
<td>24.0</td>
<td>-0.055*</td>
<td>0.956</td>
</tr>
<tr>
<td>3 months</td>
<td>18.5</td>
<td>±2.9</td>
<td>18.0</td>
<td>15.0</td>
<td>26.5</td>
<td>-0.972</td>
<td>0.331</td>
</tr>
<tr>
<td>6 months</td>
<td>18.8</td>
<td>±3.2</td>
<td>17.0</td>
<td>15.0</td>
<td>27.0</td>
<td>-1.383*</td>
<td>0.167</td>
</tr>
</tbody>
</table>

Friedman $\chi^2=79.24$ p=0.000
*Wilcoxon’s test *baseline: 15 days; *15 days: 1 month; *1 month: 3 months; *3 months: 6 months
Results

Nineteen of 20 patients completed the study, i.e. 36 eyes with different types of glaucoma (Table 1). Data are shown in absolute and relative frequencies.

Table 2 shows differences in IOP values during the study period. The differences were statistically significant immediately after the drug administration, whereafter the differences between day 15 and one month, between one month and three months, and between three months and six months were not statistically significant any more.

A constant effect of the drug could be presumed, as differences in the level of IOP between the baseline and each individual measurement were statistically significant (Table 3).

Table 3. Differences in IOP values between baseline and each measurement

<table>
<thead>
<tr>
<th></th>
<th>z*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline: 15 days</td>
<td>-5.238</td>
<td>0.000</td>
</tr>
<tr>
<td>Baseline: 1 month</td>
<td>-5.245</td>
<td>0.000</td>
</tr>
<tr>
<td>Baseline: 3 months</td>
<td>-5.239</td>
<td>0.000</td>
</tr>
<tr>
<td>Baseline: 6 months</td>
<td>-5.239</td>
<td>0.000</td>
</tr>
</tbody>
</table>

The hypotensive intraocular effect of brinzolamide expressed in percentage is presented in Table 4. The greatest hypotensive effect of the drug was recorded on the first measurement, i.e. 15 days after therapy introduction (23.6%). After six months, the hypotensive effect of the drug was 21.5%. This difference of 2.1% was not clinically significant.

The decrease in IOP values upon the administration of brinzolamide was statistically significant in both primary and secondary glaucoma. Differences in the decrease of IOP values were not statistically significant between the eyes with open angle primary glaucoma and eyes with secondary glaucoma, either at the beginning or at six months of therapy (Table 5).

Table 4. Intraocular pressure-reducing effect of brinzolamide (in %) from baseline to the end of the study

<table>
<thead>
<tr>
<th></th>
<th>Effect in %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline: 15 days</td>
<td>23.6</td>
</tr>
<tr>
<td>Baseline: 1 month</td>
<td>23.6</td>
</tr>
<tr>
<td>Baseline: 3 months</td>
<td>22.4</td>
</tr>
<tr>
<td>Baseline: 6 months</td>
<td>21.5</td>
</tr>
</tbody>
</table>

Allergy was recorded in one patient. Three patients reported adverse ocular effects. No systemic adverse effects were observed.

The examination of visual acuity, visual field and ophthalmoscopic appearance of the optic nerve head did not show any clinical differences between the beginning and the end of the study.

Discussion and Conclusion

Glaucoma is a chronic disease and longterm effects of drugs are of great clinical interest. A combination of two topical medications is common in the treatment of glaucoma. With prolonged treatment, many drugs including timolol lose some of their initial effect. The subjects included in the study were patients in whom IOT was inadequately regulated by current local therapy (17 patients with IOT >21 mm Hg) and patients with associated local discomforts such as pricking, scratching, foreign body sensation, etc. (three patients). The patients were switched to monotherapy with brinzolamide (b.i.d), and the hypotensive effect and occurrence of local or systemic side effects were monitored.

IOP was measured at baseline, and then at 15 days, one month, three months and six months of therapy in patients who were switched from previous treatment to brinzolamide. After the application of brinzolamide, differences in
the level of IOP before and on each of the following measurements were statistically significant, indicating a constant effect of the drug. The hypotensive effect of brinzolamide was statistically significant in patients with primary glaucoma as well as in those with secondary glaucoma. Initial IOP values were the only factor of clinical importance against which the prognostic value was determined for the IOP decrease achieved. Similar results were also found in other studies10-12.

Three of 19 patients had local side effects such as burning or stinging and foreign body sensation upon drug instillation. In two patients, mild conjunctival hyperemia occurred. Other authors report a relatively low percentage of local side effects, although their studies were performed in a larger number of patients10-12. Thus, it is concluded that 1.0% brinzolamide (b.i.d.), applied as monotherapy in glaucoma patients, effectively reduced IOT during the six-month study. Local side effects were rare, and there were no systemic or other harmful effects of the drug.

References

2. CAMRAS C, Brinzolamide Primary Therapy Study Group. A triple-masked, primary therapy study of the efficacy and safety of BID and TID-dosed brinzolamide 1.0% compared to TID-dosed dorzolamide 2% and BID-dosed timolol 0.5% (abstract). Invest Ophthalmol Vis Sci 1997;38 (Suppl):S560.
4. SHINDH, Brinzolamide Adjunctive Study Group. A triple masked, placebo-controlled, adjunctive study of the efficacy and safety of TID-dosed brinzolamide 1.0% compared to TID-dosed placebo when used adjunctively to timolol 0.5%. Invest Ophthalmol Vis Sci 1997;38 (Suppl):S559. (abstract)

POČETNA KLINIČKA ISKUSTVA S 1%-TNOM OČNOM SUSPENZIJOM BRINZOLAMID A (AZOPT®)

K. Novak-Lauš, Z. Mandić, R. Iveković, L. Bojić, J. Koršić i M. Zorić-Geber

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Sažetak

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