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

Katia Novak-Lauš [1], Zdravko Mandić [1], Renata Iveković [1], Lovro Bojić [2], Jadranka Koršić [1] and Mia Zorić-Geber [1]

[1]University Department of Ophthalmology, Sestre milosrdnice University Hospital, Zagreb;
[2]University Department of Ophthalmology, Split University Hospital, Split, Croatia

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 topically 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 epithelia, 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.*)[1].

Correspondence to: *Katia Novak-Lauš, M.D., M.S.* , University Department of Ophthalmology, Sestre milosrdnice University Hospital, Vinogradska c. 29, HR-10000 Zagreb, Croatia

E-mail: katianl@net4u.hr
Received March 2, 2003, accepted June 6, 2003

The 1.0% brinzolamide ophthalmic suspension is well tolerated and does not produce many of the side effects associated with CAIs when administered systemically, 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[2-5].

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

Type of glaucoma	f	%
Primary open angle glaucoma (POAG)	24	66.7
Post pars plana vitrectomy	2	5.6
Thyrotoxic orbitopathy	4	11.1
Pseudoexfoliation glaucoma	6	16.7
Total	36	100.0
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, goniscopy 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

Time point	Mean	SD	Median	Minimum	Maximum	z*	p
Baseline	23.8	±2.4	23.8	18.0	32.0		
15 days	18.2	±2.8	18.0	14.0	24.0	-5.238[a]	0.000
1 month	18.2	±2.7	18.0	13.5	24.0	-0.055[b]	0.956
3 months	18.5	±2.9	18.0	15.0	26.5	-0.972[c]	0.331
6 months	18.8	±3.2	17.0	15.0	27.0	-1.383[d]	0.167

Friedman $\chi^2=79.24$ p=0.000
*Wilcoxon's test [a]baseline: 15 days; [b]15 days: 1 month; [c]1 month: 3 months; [d]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

	z*	p
Baseline: 15 days	-5.238	0.000
Baseline: 1 month	-5.245	0.000
Baseline: 3 months	-5.239	0.000
Baseline : 6 months	-5.239	0.000

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

	Effect in %
Baseline: 15 days	23.6
Baseline: 1 month	23.6
Baseline: 3 months	22.4
Baseline : 6 months	21.5

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[6,7]. 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

Table 5. Values of intraocular pressure in primary and secondary glaucoma according to time points

	Primary open angle glaucoma					Secondary glaucoma						
	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	U*	p
Baseline	23.5	±1.2	23.3	21.0	26.0	24.5	±3.8	24.0	18.0	32.0	121	0.456
15 days	17.7	±2.5	17.0	14.0	23.0	19.1	±3.2	19.3	14.0	24.0	106	0.212
1 month	17.9	±2.5	17.8	13.5	21.5	18.9	±3.2	19.8	14.0	24.0	117	0.379
3 months	18.2	±2.4	17.8	15.0	24.0	19.1	±3.8	18.3	15.0	26.5	136	0.804
6 months	18.3	±2.9	17.0	15.0	24.0	19.6	±3.7	19.5	15.5	27.0	115.5	0.344

*Mann-Whitney U- test
Friedman χ^2=53.35 p=0.000 Friedman χ^2=26.48 p=0.000

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 studies[1,8,9].

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 patients[10-12].

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

1. SILVER L, Brinzolamide Dose-R esponse Study Group. Dose-response evaluation of the ocular hypotensive effect of brinzolamide ophthalmic suspension (Azopt ®). Surv Ophthalmol 2000;44 (Suppl 2):Sl 47-53.
2. CAMRAS C, Brinzolamide P rimary 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 -doses dorzolamide 2% and BID -dosed timolol 0.5%(abstract). Invest Ophthalmol V is Sci 1997;38 (Suppl):S560.
3. MARCH W, SILVER L, Brinzolamide L ong-Term Therapy Study Group. The long term safety and efficacy of brinzolamide(Azopt ®), a new topical carbonic anhydrase inhibitor , in patients with open-angle glaucoma and ocular hypertension. Invest Ophthalmol V is Sci 1998;39 (Suppl 4):S199. (abstract)
4. SHIN DH, Brinzolamide Adjunctive Study Group. A triple mask ed, 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 V is Sci 1997;38 (Suppl):S559. (abstract)
5. SHIN D, Brinzolamide Adjunctive Therapy Study Group. Adjunctive therapy with brinzolamide 1% ophthalmic suspension (Azopt ®) in patients with primary open-angle glaucoma or ocular hypertension maintained on timolol therapy . Surv Ophthalmol 2000;44 (Suppl 2):S163-8.
6. BOGER WP III, P ULIAFITO CA, STEINER T RF, LANGSTON DP. Long-term e xperience with timolol ophthalmic solution in patients with open-angle glaucoma. Ophthalmology 1978; 85:259-67.
7. GANDOLFI SA. R estoring sensitivity to timolol after long-term drift in primary open-angle glaucoma. Invest Ophthalmol V is Sci 1990;31:354-8.
8. KENNETH S, Brinzolamide P rimary Therapy Study Group. The efficacy and safety of brinzolamide 1% ophthalmic suspension (Azopt ®) as a primary therapy in patients with open-angle glauco - ma or ocular hypertension. Surv Ophthalmol 2000;44 (Suppl 2):S155-63.
9. LEWIS HS, Brinzolamide Dose-R esponse Study Group. Dose-response evaluation of the ocular hypotensive effect of brinzolamide ophthalmic suspension (Azopt ®). Surv Ophthalmol 2000;44 (Suppl 2):S147-53.
10. EPSTEIN DL, GRANT M. Carbonic anhydrase inhibitor side effects. Arch Ophthalmol 1997;95:1378-82.
11. LICHTER PR, NEWMAN LP , WHEELER NC, BEAL OV . Patient tolerance to carbonic anhydrase inhibitors. Am J Ophthalmol 1978;85:495-502.
12. DONOHUE EK,WILENSK YJT. Trusopt, a topical carbonic anhydrase inhibitor . J Glaucoma 1996;5:68-74.

Sažetak

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

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

Cilj rada bio je utvrditi intraok ularni hipotenzivni učinak brinzolamida 1,0% (*b.i d.*) kao monoterapije u bolesnika s primarnim i sekundarnim glaukomom. Šestmjesečno ispitivanje uključilo je 20 bolesnika od kojih je ispitivanje završilo njih 19 (jedan je bolesnik isključen zbog alergijsk e reakcije na lijek). Svi bolesnici su do tada bili na lokalnoj antiglaukomskoj terapiji. Zbog lokalnih neželjenih popratnih pojava te neodgovarajuće kontrole intraok ularnog tlaka prebačeni su na liječenje brinzolamidom 1,0% kao monoterapijom. Intraok ularni tlak je mjeren na dan zamjene, te 15 dana, 1 mjesec, 3 mjeseca i 6 mjeseci od zamjene terapije. Nakon 6 mjeseci 19 bolesnika uspješno je završilo ispitivanje. Došlo je do klinički značajnog sniženja intraok ularnog tlaka. Razlika tlaka prije (23,8 ± 2,4) i 15 dana (18,2±2,8), 1 mjesec (18,2±2,7), 3 mjeseca (18,5±2,9) i 6 mjeseci (18,8±3,2) od promjene terapije bila je statistički značajna ($p<0,001$). Odstupanje od srednje vrijednosti intraok ularnog tlaka je standardna devijacija. Kod troje bolesnika zabilježene su lokalne popratne pojave u smislu peckanja i bockanja, no nije bilo sistemskih ili drugih popratnih pojava. R ezultati ove studije ukazuju na to da je monoterapija brinzolamidom 1,0% (*b.i d.*) uspješna u regulaciji intraok ularnog tlaka u bolesnika s primarnim ili sek undarnim glaukomom.

Ključne riječi: *Inhibitori anhidraze ugljične kiseline, terapijska primjena; Inhibitori anhidraze ugljične kiseline, neželjeni učinci; Glaukom, terapija lijekovima*