The short-term IOP-lowering effect of brimonidine 0.2% and dorzolomide 2% combination in primary open-angle glaucoma

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ABSTRACT.

Purpose: **To evaluate the ocular hypotensive effect of dorzolamide 2% in primary open-angle glaucoma (POAG) patients with intraocular pressure (IOP) of at least 22 mmHg despite ongoing twice daily treatment with brimonidine 0.2%.**

Patients and Methods: **Nineteen eyes of 19 patients with POAG and IOP ≥ 22 mmHg, on twice daily brimonidine therapy, were included in the study. Intraocular pressure and adverse effects were recorded on days 2, 7, 14 and 30 after adding dorzolamide three times daily to the treatment.**

Results: **Mean pretreatment IOP was 27.6 ± 2.2 mmHg. This decreased to 24.2 ± 2.2 mmHg after a mean duration of 23.8 ± 12.1 days. After dorzolamide was added to the treatment, mean IOP was 20.8 ± 2.3 mmHg on day 2, 19.3 ± 2.2 mmHg on day 7, 18.0 ± 2.5 mmHg on day 14 and 17.2 ± 2.3 mmHg on day 30. The differences between pre- and post-treatment IOP values were statistically significant ($p < 0.0001$, anova test).**

Conclusion: **Dorzolamide administered three times daily has significant additive ocular hypotensive effect in POAG patients whose IOP is elevated despite ongoing treatment with brimonidine.**

Key words: brimonidine – dorzolamide – primary open-angle glaucoma

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Brimonidine tartrate is a highly selective α-2 adrenergic agonist ocular hypotensive drug. It has intraocular pressure (IOP) lowering characteristics similar to those of other α-2 adrenergic agonists, acting by reducing aqueous humour production and increasing uveoscleral outflow (Greenfield et al. 1997). It has been popularly used as an adjunctive agent and is emerging as a potential first line therapy for primary open-angle glaucoma (POAG) with IOP-lowering efficacy comparable to that of timolol at peak, but without the adverse cardiopulmonary side-effects of timolol (Schuman 1996; Stewart et al. 2000a).

Dorzolamide is a well-known topical carbonic anhydrase inhibitor which decreases aqueous humour secretion by inhibiting carbonic anhydrase isoenzyme-II in the ciliary process of the eye (Boyle et al. 1998). Used as monotherapy, dorzolamide reduces IOP by up to 26% (Lippa et al. 1991). It has eliminated most of the systemic symptoms commonly associated with acetozolamide. When used three times daily as monotherapy, dorzolamide has been found to have levels of efficacy and safety in POAG and ocular hypertensive patients similar to those of brimonidine (Stewart et al. 2000a).

Glaucoma patients may require more than one medication for IOP control. To our knowledge, the combined effects of dorzolamide and brimonidine have not been studied previously. In this study, we evaluated the short-term additive IOP-lowering effect of dorzolamide 2% in patients with POAG whose IOP was inadequately controlled by brimonidine 0.2%.

Patients and Methods

This study comprised 19 eyes of 19 POAG patients with IOP ≥ 22 mmHg despite ongoing twice daily treatment with brimonidine 0.2% (Alphagan, Allergan, California, USA). All the patients were attending the Ophthalmology Department of the Medical Faculty of Afyon Kocatepe University and underwent a complete ocular examination. Glaucoma was defined as IOP higher than 21 mmHg without medication, measured on at least two consecutive occasions separated by an interval of at least 2 hours, as well as glaucomatous visual field or optic disc changes. Pretreatment IOP ranged from 24 to 32 mmHg and was measured 1 day before beginning treatment with brimonidine. Each subject had at least three IOP measurements taken before treatment commenced. Goldmann applanation tonometry was used for IOP measurements. All measurements were made between 15.00 and 16.00 hours. Exclusion criteria included: any history of chronic

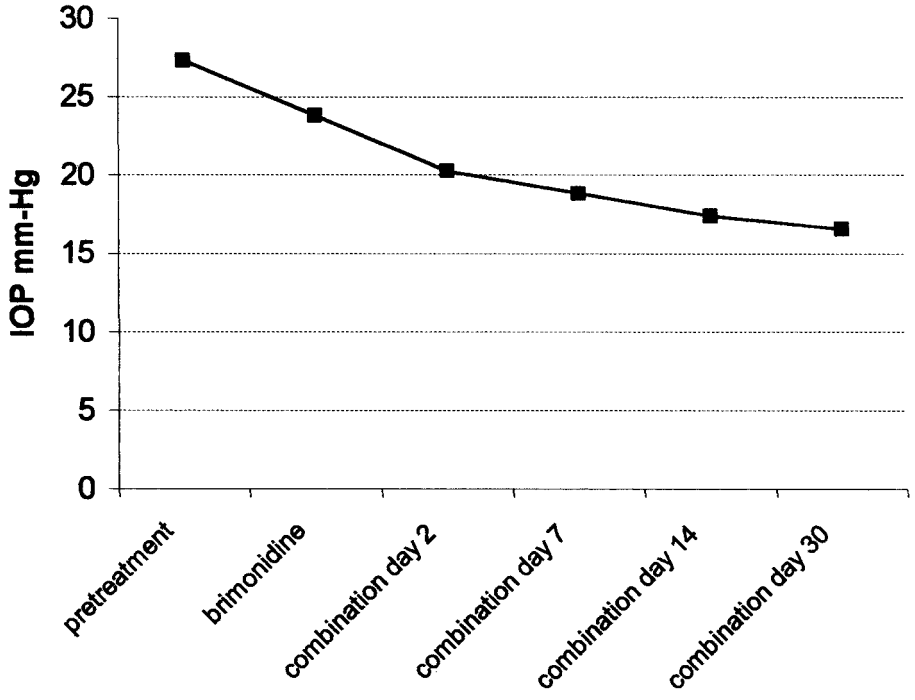

Fig. 1. Mean IOP values during the study.

or recurrent inflammatory eye disease, ocular trauma, ocular infection, severe retinal disease, previous intraocular or laser surgery, corneal abnormality preventing reliable applanation tonometry, hypersensitivity to medications used in the study, use of any systemic medication that might effect IOP and unstable cardiopulmonary disease.

Written informed consent was obtained from each patient. The research followed the tenets of the Declaration of Helsinki.

During the study, brimonidine was administered at 08.00 and 20.00 hours and dorzolamide was administered at 08.00, 16.00 and 24.00 hours.

Intraocular pressure was measured on days 2, 7, 14 and 30 after dorzolamide 2% (Trusopt, Merck, Pennsylvania, USA), administered three times daily, was added to the ongoing twice daily treatment with brimonidine 0.2%.

The primary efficacy variable was IOP. This was analysed by analysis of variance (ANOVA). A Tukey–HSD test was used to determine the significance of differences between the means of IOPs. P-values <0.05 were considered statistically significant. Statistical analysis was performed with SPSS VERSION 10.0 (SPSS Inc., Chicago, USA).

Results

The study included 19 POAG patients, of whom eight were women and 11 were men. Their mean age was 56.8 ± 11.9 years (range 41–75 years). All patients were white. Mean pretreatment IOP was 27.6 ± 2.2 mmHg. After treatment with brimonidine twice daily for a mean duration of 23.8 ± 12.1 days (range 15–54

Table 1. Mean IOP and mean changes in IOP during the study. Percentage of IOP with respect to pretreatment IOP shown in parenthesis.

	IOP (mmHg)		p	Change in IOP (mmHg)
Pretreatment	27.6 ± 2.2			
Brimonidine	24.2 ± 1.8	(88%)	0.0001	3.4 ± 1.9*
Brimonidine + dorzolamide day 2	20.8 ± 2.3	(75%)	0.0001	3.4 ± 1.3*
Brimonidine + dorzolamide day 7	19.3 ± 2.2	(70%)	0.0003	1.5 ± 0.8
Brimonidine + dorzolamide day 14	18.0 ± 2.5	(65%)	0.0015	1.3 ± 1.2
Brimonidine + dorzolamide day 30	17.2 ± 2.3	(62%)	0.001	0.8 ± 0.6

* $p < 0.05$

Table 2. Numbers of patients reporting ocular and systemic side-effects.

Symptoms	Brimonidine	Brimonidine + dorzolamide
Stinging/burning	4	4
Itching	2	1
Conjunctival hyperaemia	0	2
Irritation	0	1
Dry mouth	2	2
Fatigue	2	1
Bitter taste	0	1

days), IOP decreased to 24.2 ± 1.8 mmHg. After dorzolamide was added to treatment, mean IOP was 20.8 ± 2.3 mmHg on day 2, 19.3 ± 2.2 mmHg on day 7, 18.0 ± 2.5 mmHg on day 14 and 17.2 ± 2.3 mmHg on day 30. The differences between IOP values were statistically significant ($p < 0.0001$, ANOVA test) (Table 1, Fig. 1). The IOP values between all consecutive visits were statistically significantly different ($p = 0.0001$ for pretreatment brimonidine treatment to day 2 of brimonidine dorzolamide combination, $p = 0.0003$ for day 2 to day 7 of combination treatment with brimonidine and dorzolamide, $p = 0.0015$ for day 7 to day 14 of combination treatment with brimonidine and dorzolamide, $p = 0.001$ for day 14 to day 30 of combination treatment with brimonidine and dorzolamide, Tukey–HSD test).

The changes in IOP values were also compared. The decreases in IOP between treatment with brimonidine only and 2 days after adding dorzolamide to the treatment were significantly greater than subsequent IOP decreases ($p < 0.05$,-ANOVA test) (Table 1).

Intraocular pressure ≥ 20 mmHg was recorded in 12 patients on day 2, in seven patients on day 7, in four patients on day 14 and in three patients on day 30.

Ocular and systemic side-effects are shown in Table 2. All events were reported as mild. No serious side-effects were observed.

Discussion

Glaucoma is a progressive optic neuropathy with characteristic optic nervehead changes and decreases in retinal sensitivity that lead to visual loss. Once the disease is diagnosed, treatment is required to stop progressive damage (Fechtner & Weinreb 1994; McKellan 1995). Generally, medical treatment is the first therapeutic approach and lowering IOP is the only established medical treatment for POAG. There is increasing evidence that reducing IOP as much as possible improves the likelihood of delaying or halting progression of optic nerve damage and visual field loss (Sherwood et al. 1993; Boyle et al. 1998; Emmerich 2000). Various antiglaucoma agents are used for the treatment of POAG. In a large number of patients, a single therapeutic agent may be unable to maintain a desirable level of IOP. In these patients a second agent may be added to the treatment.

This study was undertaken to evaluate the IOP-lowering effect of dorzolamide when added to brimonidine. To our knowledge, this is the first study to demonstrate the additional IOP-lowering effect of dorzolamide in patients already receiving brimonidine treatment. One limitation of our study was that it did not include a negative control group. As our subjects had POAG, not ocular hypertension, and their IOP levels were 23–28 mmHg (mean 24.2 ± 1.8 mmHg) after brimonidine treatment for 15–54 days (mean 23.8 ± 12.1 days), we added dorzolamide.

Brimonidine and dorzolamide, used individually as monotherapy, have similar IOP-lowering effects in patients with POAG and ocular hypertension (Stewart et al. 2000a). Dorzolamide has been reported to reduce IOP by 20% when added to timolol, indicating good additive effects of dorzolamide and timolol (Hartenbaum 1996; Emmerich 2000). As brimonidine decreases IOP not only by reducing aqueous humour production but also by increasing uveoscleral outflow, brimonidine and dorzolamide may be an effective combination. In our study, IOP decreased by 29% 30 days after the addition of dorzolamide. It has also been suggested that brimonidine, as well as lowering IOP, has a potentially beneficial neuroprotective effect in the management of glaucoma (Burke & Schwartz 1996; Yoles et al. 1999). Stewart et al. (2000b) evaluated dorzolamide as adjunctive therapy with various β-blockers in POAG and ocular hypertension patients and observed a mean IOP decrease of 3.1 mmHg at the end of 3 months.

In conclusion, the results of our study show that dorzolamide causes a further statistical reduction in IOP in glaucomatous eyes that receive ongoing treatment with brimonidine.

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