Effect of 2% dorzolamide on retinal blood flow: a study on juvenile primary open-angle glaucoma patients already receiving 0.5% timolol

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Aim

To investigate whether dorzolamide modifies peripapillary retinal haemodynamics in juvenile primary open-angle glaucoma (JPOAG) patients treated with timolol.

Methods

In 40 JPOAG subjects, before and after dorzolamide coadministration with timolol, the following examinations were achieved: intraocular pressure (IOP), blood pressure (BP), ocular perfusion pressure (OPP), heart rate (HR), visual field and retinal flowmetry.

Results

Adjunctive therapy with dorzolamide induced the following modifications: IOP reduction [1.75 mmHg, 95% confidence interval (CI) 1.23, 2.26; $P < 0.05$], OPP increase (5.09 mmHg, 95% CI 2.97, 7.20; $P < 0.02$) and retinal blood flow improvement (35.0 arbitrary units, 95% CI 12.20, 57.80; $P < 0.03$). BP, HR and visual field indices did not change.

Conclusions

Dorzolamide, in association or in fixed combination with timolol, significantly improves retinal blood flow in JPOAG patients.

Introduction

The term glaucoma indicates a heterogeneous group of chronic ocular disorders, in which damage to the optic nerve head (ONH) is related to different synergistic factors, such as overcoming of the critical intraocular pressure (IOP), impairment of ONH blood supply and neurotoxicity [1]. The most frequent form is primary

open-angle glaucoma (POAG) [2], characterized by increased IOP (with maximal values >21 mmHg), typical ONH changes, visual field loss and open/normal irido-corneal angle. POAG patients aged <40 years at the time of diagnosis are classified as suffering from juvenile-onset POAG (JPOAG) [3].

Timolol, a topical nonselective β -blocker, inhibits

aqueous humour secretion by about 25% with an IOP fall of a similar degree; this action is obtained by decreasing β -adrenergic tone and inducing ciliary arteriolar vasoconstriction. Dorzolamide, a topical carbonic anhydrase inhibitor (CAI), decreases IOP by about 18%, through a block of the carbonic anhydrase enzyme at the level of the ciliary body. In POAG patients timolol does not seem to alter ocular haemodynamics, whereas dorzolamide increases retinal microcirculation and ocular blood flow (OBF) [4, 5]. We therefore performed a study to investigate the effect of 2% dorzolamide on IOP, OBF and visual field in JPOAG patients who were already receiving 0.5% timolol.

Methods

Subjects

The study included 80 eyes of 40 consecutive White subjects with bilateral JPOAG (20 men, 20 women; mean age 40.81 ± 8.12 years; range 18–50 years). Both eyes were examined but only the data recorded from the right eye of each patient were used for statistical evaluations. The inclusion criteria were: presence of JPOAG in both eyes of patients aged between 16 and 40 years at the time of diagnosis; at least 6-month treatment with 0.5% timolol eyedrops b.i.d.; visual field defect (i.e. a localized field defect with at least three adjacent non-edge points depressed >5 dB from the average normal value for age, and a nucleus of at least one point depressed 10 dB from the normal value).

Exclusion criteria were: ametropia >4 dioptres; corneal disorders and/or ocular infections; previous ocular trauma, surgical procedures and/or laser treatment within

the last 12 months; any other eye disease influencing OBF; uncontrolled systemic disease; pregnancy, planning a pregnancy or breastfeeding; taking of systemic β -blockers and/or CAIs; recognized hypersensitivity to one of the study compounds or their components. The use of caffeine and nicotine was avoided 12 h before the clinical checks, because these substances are known to affect OBF. Approval from the local Ethics Committee was obtained and all subjects gave written informed consent.

Study design

In all timolol-treated JPOAG patients, a baseline determination (T0) of systolic and diastolic blood pressure (SBP and DBP, respectively), heart rate (HR), IOP, visual field, and OBF was performed. The same examinations were repeated 1 month later (T1) with patients continuing 0.5% timolol b.i.d., to confirm baseline findings. At this time, 2% dorzolamide b.i.d. was bilaterally coadministered with 0.5% timolol. All parameters were recorded after 1 month of this regimen (T2). During the third month, the two separate compounds were replaced by the fixed 0.5% timolol and 2% dorzolamide combination b.i.d. and, at the end of this period, all measurements were registered again (T3) (Table 1).

Study methods

SBP and DBP were determined by a Riva-Rocci sphygmomanometer (Rudolf Riester GmbH & Co., Jungingen, Germany). IOP was measured employing a Goldmann applanation tonometer (Haag-Streit, Bern, Switzerland). Ocular perfusion pressure (OPP) was cal-

Table 1

Schedule employed in the course of the study.

Time	T0 (baseline)	T1 (1st month)	T2 (2nd month)	T3 (3rd month)
Informed consent	☐			
Intraocular pressure	☐	☐	☐	☐
Visual acuity	☐			
Anterior segment examination	☐			
Fundus examination	☐			
Blood pressure	☐	☐	☐	☐
Heart rate	☐	☐	☐	☐
Scanning laser Doppler flowmetry	☐	☐	☐	☐
Visual field	☐	☐	☐	☐
0.5% timolol
2% dorzolamide
Timolol/dorzolamide fixed combination

culated using the formula: $OPP = (1/3 \text{ SBP} + 2/3 \text{ DBP}) \times 2/3 - IOP$. Visual field was recorded with a Humphrey Field Analyser (30-2 full-threshold white-on-white program). Scanning laser Doppler flowmetry (Heidelberg Retina Flowmeter, HRF; Heidelberg Engineering GB, Dossenheim, Germany) was employed to measure OBF in rim (RBF), temporal (TRPBF) and nasal retinal peri-papillary (NRPBF) areas. The HRF data were analysed using the Automatic Full-Field Perfusion Image Analyser (AFFPIA) program.

Data analysis

The Statgraphics V4 statistical package (STSC Inc., Rockville, MD, USA) was used for statistical analysis. One-way analysis of variance (ANOVA) and coefficient of correlation were used; a probability of $P < 0.05$ was considered statistically significant.

Results

At the T1 check, every variable considered showed no statistically significant difference with respect to T0

values. At the T2 check, after 1-month coadministration of dorzolamide/timolol, a significant IOP reduction occurred [1.75 mmHg, 95% confidence interval (CI) 1.23, 2.26; $P < 0.05$], without variations in SBP/DBP and HR. An improvement of OPP (5.09 mmHg, 95% CI 2.97, 7.20; $P < 0.02$) and HRF parameters (RBF, TRPBF and NRPBF) was observed (35.0 arbitrary units, 95% CI 12.20, 57.80, $P < 0.03$; 40.8 arbitrary units, 95% CI 24.92, 56.68, $P < 0.03$; and 66.7 arbitrary units, 95% CI 55.5, 79.88, $P < 0.04$, respectively). No significant variation of visual field indices (mean deviation and correct pattern standard deviation) occurred. At the T3 check, the 1-month instillation of timolol/dorzolamide fixed combination gave results similar to those recorded when the two compounds were administered separately. All these data are summarized in Table 2. Negative correlations were found between the IOP decrease and the increase of RBF, NRPBF and TRPBF ($r = -0.945$, $P = 0.055$; $r = -0.982$, $P = 0.018$; $r = -0.987$, $P = 0.013$, respectively). SBP and DBP showed

Table 2

Mean values $\pm$ SD (with 95% CI) of all recorded parameters in each right eye of the 40 juvenile primary open-angle glaucoma patients

	T0 (baseline)	T1 (1st month)	T2 (2nd month)	T3 (3rd month)
IOP (mmHg)	16.06 $\pm$ 2.05 (15.40, 16.70)	15.92 $\pm$ 1.32 (15.50, 16.34)	14.31 $\pm$ 1.12 (13.95, 14.65)§	14.04 $\pm$ 1.17 (13.67, 14.41)§
SBP (mmHg)	126 $\pm$ 8.73 (123.24, 128.76)	127 $\pm$ 8.44 (124.33, 129.67)	125 $\pm$ 8.32 (122.37, 127.63)	128 $\pm$ 9.54 (124.98, 131.02)
DBP (mmHg)	74 $\pm$ 7.85 (71.52, 76.48)	76 $\pm$ 7.72 (73.56, 78.44)	73 $\pm$ 8.13 (70.43, 75.57)	75 $\pm$ 7.97 (72.48, 77.52)
OPP (mmHg)	40.82 $\pm$ 6.24 (38.85, 42.79)	40.07 $\pm$ 5.54 (38.31, 41.83)	45.91 $\pm$ 7.28 (43.61, 48.21)*	47.73 $\pm$ 6.26 (45.75, 49.71)§
HR (beats/min)	65 $\pm$ 2.21 (64.30, 65.70)	66 $\pm$ 2.01 (65.36, 66.64)	66 $\pm$ 1.82 (65.42, 66.58)	64 $\pm$ 1.75 (63.45, 64.55)
RBF (AU)	205.3 $\pm$ 80.02 (179.99, 230.61)	197.4 $\pm$ 71.23 (174.88, 219.92)	240.3 $\pm$ 65.26 (219.66, 260.94)†	232.5 $\pm$ 86.42 (205.17, 259.83)†
TRPBF (AU)	271.3 $\pm$ 46.8 (256.50, 286.10)	275.9 $\pm$ 38.4 (263.75, 288.05)	312.1 $\pm$ 54.6 (294.83, 329.37)†	309.4 $\pm$ 41.8 (296.18, 322.62)†
NRPBF (AU)	292.4 $\pm$ 34.2 (281.59, 303.21)	302.6 $\pm$ 53.7 (285.61, 319.59)	360.1 $\pm$ 43.3 (346.41, 373.79)‡	353.8 $\pm$ 40.9 (340.87, 366.73)‡
MD (dB)	-3.3 $\pm$ 1.91 (-3.90, -2.70)	-3.0 $\pm$ 1.65 (-3.53, -2.49)	-2.9 $\pm$ 1.72 (-3.44, -2.36)	-3.1 $\pm$ 1.51 (-3.58, -2.62)
CPSD (dB)	5.01 $\pm$ 3.42 (3.93, 6.09)	5.12 $\pm$ 3.98 (3.86, 6.38)	4.5 $\pm$ 2.68 (3.65, 5.35)	4.2 $\pm$ 3.12 (3.21, 5.19)

IOP, Intraocular pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; OPP, ocular perfusion pressure; HR, heart rate; RBF, rim blood flow; TRPBF, temporal retinal peripapillary blood flow; NRPBF, nasal retinal peripapillary blood flow; AU, arbitrary units; MD, mean deviation; CPSD, correct pattern standard deviation; dB = decibel. One-way analysis of variance (ANOVA) was used for statistical analysis; the comparison was performed vs. baseline: * $P < 0.02$; † $P < 0.03$; ‡ $P < 0.04$; § $P < 0.05$.

no significant correlation with IOP, RBF, NRPBF or TRPBF, as well as between IOP and OPP.

Discussion

The ONH haemodynamics depends on the relationship among IOP, SBP/DBP, vascular resistance and autoregulation. Several studies have indicated that OBF instability, due to a disturbed autoregulation in the context of a general vascular dysregulation, might contribute to glaucomatous optic neuropathy [1, 6]. Thus, considerable interest has developed in topical CAIs that, besides their IOP-reducing action, are also able to exert a beneficial influence on ocular perfusion [1, 6]. In our JPOAG population, dorzolamide produced a significant IOP decrease without influencing SBP/DBP and, consequently, increasing the calculated OPP both during its coadministration and in fixed combination with timolol. Moreover, this compound enhanced the HRF parameters, resembling the data recently observed by Fuchs-jager-Mayrl and coworkers in patients with POAG or ocular hypertension [5].

At present, HRF can be considered the most useful approach to perform a high-definition topography of perfused vessels at the level of the peripapillary retina. The complexity of HRF measurements results in various intrinsic limitations of this diagnostic tool, but a quite satisfactory reproducibility has been reported by several authors [7–9]. However, although the HRF technique is constantly improving and the AFFPIA program may be helpful to interpret the data, current devices are able to measure only the retinal capillary blood flow, which is just a component of the OBF and is not wholly representative of the ONH blood flow.

An important piece of evidence emerging from our study is that JPOAG patients, despite an adequately controlled IOP, showed an OPP level known to reliably increase the risk of optic nerve damage [6]. This perfusion impairment could be secondary to the chronic timolol administration, which has been hypothesized to induce autoregulation changes by a tendency to iatrogenic vasospasm [1, 6, 10]. On the other hand, the JPOAG status itself could also be responsible for vascular dysregulation [1, 6]. Thus, during the management of the disease, although the IOP lowering alone induces an improvement in OBF, it may be beneficial to prescribe compounds able to reduce IOP also directly upgrading ONH haemodynamics. Therefore, the evidence that dorzolamide improves OPP and HRF parameters, even in patients with a target IOP apparently attained, could speculatively provide a rationale for the use of topical CAIs in selected cases of chronic JPOAG, mainly taking

into account: (i) the European Glaucoma Society guidelines, which indicate that the goal of any antiglaucoma therapy is an adequate preservation of visual function for the expected lifetime of every patient [4]; (ii) the recent findings of Jeppesen and coworkers, who have demonstrated the presence of an age-dependent worsening in myogenic response of retinal arterioles [11].

Our results support a favourable effect of dorzolamide, even if the present flowmeter technology does not allow discrimination of the influence of IOP reduction on the blood flow. Comparative prospective randomized studies, with a longer follow-up, will be necessary to ascertain the effect of the topical CAIs on visual field indices of JPOAG patients.

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