Effect of Dorzolamide and Timolol on Ocular Pressure: Blood Flow Relationship in Patients with Primary Open-Angle Glaucoma and Ocular Hypertension

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PURPOSE. The authors have reported previously that a study population, consisting of patients with glaucoma and ocular hypertension, is characterized by an impaired association between ocular blood flow parameters and systemic blood pressure, indicative of abnormal autoregulation. Here they report on the effects of dorzolamide and timolol on ocular pressure/flow relationships to test the hypothesis that these drugs improve autoregulation.

METHODS. One hundred forty patients with primary open-angle glaucoma or ocular hypertension were included in a clinical trial in a controlled, randomized double-masked study in two parallel groups. Seventy patients were randomly assigned to receive timolol, and 70 patients were randomly assigned to receive dorzolamide for a 6-month period. Scanning laser Doppler flowmetry was used to measure blood flow in the temporal neuroretinal rim and the cup of the optic nerve head. Pulsatile choroidal blood flow was assessed using laser interferometric measurement of fundus pulsation amplitude. The association between blood flow parameters and systemic blood pressure was compared before and after the 6-month treatment period.

RESULTS. Before treatment a significant association was observed between ocular blood flow parameters and systemic blood pressure in both parallel groups (r = 0.23–0.42). All regression lines between ocular hemodynamic parameters and systemic blood pressure were less steep after treatment with either dorzolamide or timolol (r = 0.03–0.24).

CONCLUSIONS. The present study indicates that intraocular pressure reduction with timolol or dorzolamide is associated with normalization of the ocular pressure/flow relationship. Whether this is related to the beneficial effects of IOP-lowering therapy in glaucoma remains to be established. (ClinicalTrials.gov number, NCT00991822.) (Invest Ophthalmol Vis Sci. 2010;51:1289–1296) DOI:10.1167/iovs.09-3827

The exact nature of the role of ocular perfusion abnormalities in the pathogenesis of glaucoma is still a matter of debate. Several large-scale studies have found that low ocular perfusion pressure and low blood pressure are risk factors for the prevalence, incidence, and progression of primary open-angle glaucoma (POAG).1-3 Data from the Rotterdam study indicate that retinal vessel diameters are not related to incident POAG.4 Whether retinal vessel diameters are, however, a good indicator of retinal perfusion status in patients with glaucoma is unclear. Nevertheless several authors have concluded from such measurements that reduced ocular blood flow in glaucoma may be the consequence rather than the cause of optic nerve head remodeling and loss of retinal ganglion cells.

In recent years it has been hypothesized that POAG is associated with vascular dysregulation.5,6 This dysregulation is unlikely to be a consequence of the disease process and leads to an abnormal blood flow response in the face of challenges such as changes in perfusion pressure. Hence, abnormal autoregulation can be considered a sign of vascular dysregulation in POAG. To prove that patients with POAG show abnormal autoregulation in the ocular vascular bed is, however, far from easy, because it involves experimental changes in perfusion pressure, which are difficult to induce in an elderly population. An alternative is to study pooled data and to perform linear correlation analysis between blood flow and pressure data.7 The regression slope and the regression coefficient can then be used as objective measures of static autoregulation.

We have recently shown that untreated patients with early POAG or ocular hypertension have an increased regression slope between systemic blood pressure and choroidal and optic nerve blood flow parameters.8 These data stem from a double-masked, placebo-controlled, crossover trial comparing the ocular hemodynamic effects of timolol and dorzolamide. The effects of 6-month monotherapy with either timolol or dorzolamide on optic nerve head and choroidal blood flow parameters were reported previously.9 Although dorzolamide increased all ocular hemodynamic variables by approximately 10%, timolol had no significant effect. In the present paper we report the effects of timolol and dorzolamide on the relationship between ocular blood flow parameters and systemic blood pressure arising from the same clinical trial.

PATIENTS AND METHODS

Patients

Approval for the study was obtained from the Ethics Committee of Vienna University School of Medicine. The study followed the guidelines of Good Clinical Practice and the Declaration of Helsinki, including the current revisions. One hundred forty patients with POAG or ocular hypertension (OHT) were included. For the sample size calculation, which was based on the variability of the Heidelberg Retina Flowmetry (HRF) data in our laboratory (52% in patients with POAG as calculated from monthly measurements over 6 months; unpublished data), an α-level of 0.05 and a β-level of 0.2 were selected. Differences...
of <10% between treatment groups were considered to be clinically irrelevant in the present study. Hence, the sample size calculation gave a total number of 127 subjects, but 140 patients were included based on the anticipated dropout rate.

Inclusion and exclusion criteria as well as baseline characteristics of the participating subjects have been reported in detail. Briefly, patients with either POAG or OHT with an untreated IOP ≥ 21 mm Hg (documented on at least at three different occasions) in at least one eye were included. All patients were eligible for antiglaucoma monotherapy. A washout period for previous antiglaucoma treatment of 2 weeks was scheduled for all patients. Patients with exfoliation glaucoma, pigmentary glaucoma, history of acute-angle closure, mean deviation (MD) of visual field testing (Humphrey 30-2 program) > −10, or intraocular surgery or argon laser trabeculoplasty within the previous 6 months, ocular inflammation or infection within the previous 3 months, bradycardia (heart rate < 50 bpm), second- and third-degree heart block, asthma bronchiale, chronic obstructive pulmonary disease, congestive heart failure, severe renal impairment (creatinine clearance < 1.8 L/h), history of hypersensitivity to one of the study drugs or drugs with similar chemical structure, history of non-IOP responder to topical β-blockers or topical carbonic anhydrate inhibitors, and pregnancy were excluded from participation. Differentiation between POAG and patients with OHT was based on the criteria of the Ocular Hypertension Treatment Study. An abnormal visual field was accordingly defined as a glaucoma hemifield test result outside normal limits, corrected-pattern SD P < 0.05, or both. The study was performed at the Departments of Clinical Pharmacology and Ophthalmology at the Medical University of Vienna.

Protocol

The study protocol has been described in detail. A prestudy screening was scheduled in the 2 weeks before the start of the study, checking for inclusion and exclusion criteria. If at least one eye of the patient was eligible for study purposes, a baseline visit was scheduled. Two weeks after the baseline visit, another visit was scheduled dividing the patients into responders and nonresponders. Responders were defined as patients whose IOP was ≤ 19 mm Hg or who had an IOP decrease compared with baseline IOP ≥ 25% in the index eye and who continued the study as scheduled. Nonresponders or patients who did not tolerate the study medication crossed over to the alternative treatment and were scheduled for a next visit 2 weeks later. At this visit patients were again divided into responders and nonresponders. Nonresponders for both medications were finally excluded from the study, whereas patients who responded to the second antiglaucoma drug continued the study as scheduled. Three and 6 months after the baseline day, additional visits were scheduled. All hemodynamic outcome variables and IOP were assessed during these visits. At the last visit a visual field test and an ophthalmic examination were performed again. A deviation of ≤ ± 3 days was allowed for the 2-week visit, and a deviation of ≤ ± 1 week was allowed for the other visits.

Summary of Previously Published Data

Baseline characteristics of the study population and effects of the study drugs have been presented. Both study groups were matched with regard to systemic blood pressure, intraocular pressure, and ocular hemodynamic parameters at baseline. Using scanning laser Doppler flowmetry, 125 (89%) and 127 (91%) blood flow readings, with a coefficient of variation of 10% (Rim BF, 8.5% ± 1.6% [P < 0.001] vs. timolol; CupBF, 13.5% ± 2.5% [P < 0.001] vs. timolol; FPA, 8.9% ± 1.3% [P < 0.001] vs. timolol), timolol did not affect them. Three patients appeared at the baseline visit only and were thereafter lost to follow-up. These patients were not included in the analysis. Five patients changed from the timolol to the dorzolamide group after the first two weeks of treatment, and 18 patients changed from the dorzolamide to the timolol group. These 23 patients remained on the alternative medication. After the baseline visit 12 patients were lost to follow-up.

Methods

Scanning Laser Doppler Flowmetry. The principles of laser Doppler flowmetry (Heidelberg Retina Flowmeter; Heidelberg Engineering, Heidelberg, Germany) have been described in detail by Bonner and Nossal. Briefly, vascularized tissue is illuminated by coherent laser light. Scattering by moving red blood cells (RBCs) leads to a frequency shift in the scattered light. In contrast, static scatterers in tissue do not change light frequency but lead to randomization of light directions impinging on RBCs. This light diffusing in vascularized tissue leads to a broadening of the spectrum of scattered light (Doppler shift power spectrum [DSPS]). From this DSPS, the mean RBC velocity (vel), the blood volume (vol), and the blood flow (Flow) can be calculated in relative units. These parameters are calculated from the backscattered light for each point during the scanning process. The procedure of data sampling and the confocal optical system have been described in detail. The line sample frequency is 4000 Hz, and frequencies <125 Hz are excluded for fast Fourier transform.

From calculated RBC velocity, blood volume, and blood flow, a two-dimensional map is created of retinal and optic nerve perfusion. Hence, these parameters can be quantified in relative units for any image point. In the present study one 10 × 10 pixel area (100 × 100 μm) in the cup of the optic disc (CupBF) and one 20 × 20 pixel area (200 × 200 μm) at the temporal neuroretinal rim (RimBF) were chosen for calculation of hemodynamic parameters. Selection of the measurement area was based on the method described by Nicolaie et al. The same method was also used to ensure that the same region was used in consecutive measurements. The neuroretinal rim was measured from images focused on the superficial retina. The cup was measured from images focused on the lamina cribrosa. Measurements were performed in regions without major surface vessels.

Reproducibility is a critical issue with scanning laser Doppler flowmetry. Hence, at least two recordings were taken, and the mean of the two values from the best images obtained was calculated. Only flow readings with a coefficient of variation of < 20% were included in the analysis.

Laser Interferometric Measurement of Fundus Pulsation. Pulse synchronous pulsations of the eye fundus were assessed by laser interferometry. The method is described in detail by Schmetterer et al. Briefly, the eye is illuminated by the beam of a single-mode laser diode with a wavelength (λ) of 783 nm. The light is reflected at both the front surface of the cornea and the fundus. The two re-emitted waves produce interference fringes from which the distance changes between cornea and retina during a cardiac cycle can be calculated. Distance changes between cornea and retina lead to a corresponding variation of the interference order (ΔN(t)). This change in interference order can be evaluated by counting the fringes moving inward and outward during the cardiac cycle. Changes in optical distance (ΔL(t), corresponding to the cornea-retina distance changes, can then be calculated by ΔL(t) = ΔN(t) · λ/2. The maximum distance change is called fundus pulsation amplitude (FPA) and estimates the local pulsatile blood flow. Measurements of FPA were performed in the fovea to assess pulsatile choroidal blood flow. Again, two measurements were performed at each fundus location, and the mean of the two measurements was calculated. FPA values with a coefficient of variation > 20% were not included for analysis.

Noninvasive Measurement of Systemic Hemodynamics. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured on the upper arm by an automated oscillometric device. Mean arterial pressure (MAP) was calculated as ½ SBP + ½ DBP. Pulse rate (PR) was automatically recorded from a finger pulse oxymetric device (HP-CMS patient monitor; Hewlett Packard, Palo Alto, CA). Ocular perfusion pressure in the sitting position was calculated as ½ × MAP − IOP.
Statistical Analysis

Linear regression analysis was performed to determine the correlation between MAP and ocular perfusion pressures and ocular hemodynamic parameters in both study groups. This was performed separately for data assessed at the baseline visit and for data assessed at the 6-month visit. Data are presented as mean ± SD. The level of significance was set to $P = 0.05$.

RESULTS

MAP/flow relationships at baseline are depicted in Figure 1. Data are separately presented for patients who received dorzolamide ($n = 20$ patients with POAG, $n = 37$ patients with OHT) and patients who received timolol ($n = 29$ patients with POAG, $n = 54$ patients with OHT). A significant association was found between all ocular hemodynamic parameters and

FIGURE 1. Correlations between FPA and MAP, CupBF and MAP, and RimBF and MAP before (left) and after (right) the administration of dorzolamide.
systemic blood pressure ($r = 0.23–0.42$). The association between HRF parameters and blood pressure was higher than the association between FPA and blood pressure. MAP/flow relationships after 6 months of treatment are shown in Figure 2. After administration of both timolol and dorzolamide, there was a reduction in the correlation coefficient between ocular blood flow variables and blood pressure ($r = 0.05$ and 0.24).

Ocular perfusion pressure/flow relationships at baseline are depicted in Figure 3. A significant association was found between all ocular hemodynamic parameters and ocular perfusion pressure ($r = 0.24$ and 0.41). Ocular perfusion pressure/flow relationships after 6 months of treatment are shown in Figure 4. After administration of both timolol and dorzolamide, there was a reduction in the correlation coefficient between ocular blood flow variables and ocular perfusion pressure ($r = 0.06$ and 0.19).

These results were obtained though neither of the two drugs influenced blood pressure significantly and the ocular
hypotension induced by dorzolamide and timolol were comparable. Timolol-induced changes in IOP were comparable between patients with POAG (−21.5% ± 12.3%) and patients with OHT (−23.5% ± 12.8%; \( P = 0.52 \) between groups). Dorzolamide-induced changes in IOP were also comparable between patients with POAG (−18.7% ± 12.3%) and patients with OHT (−20.8% ± 12.6%; \( P = 0.46 \) between groups). Similarly, no difference was observed in the ocular hemodynamic responses between patients with POAG and patients with OHT with either timolol or dorzolamide (data not shown).

**DISCUSSION**

We have previously reported that the population included in this clinical study showed increased regression slopes and increased
regression coefficients between blood pressure and ocular blood flow parameters, indicative of abnormal autoregulation. For this report, data were analyzed separately for the timolol and the dorzolamide groups, and a significant correlation was found in both parallel groups for all blood flow parameters measured at baseline. The aim of this evaluation was to examine whether this relation was altered after 6-months treatment with either timolol or dorzolamide. Both drugs were capable of reducing the association between ocular blood flow parameters and blood pressure, indicating reduced vascular dysregulation. This effect was seen despite the fact that only dorzolamide, but not timolol, increased blood flow in the present trial.

With the linear regression method, the regression slope and the regression coefficient can be considered objective measures of static autoregulation. If both values are close to zero, data indicate perfect autoregulation. The steeper the regression slope and the higher the regression coefficient, the more impaired is autoregulation within the study population. Data

Figure 4. Correlations between FPA and ocular perfusion pressure (OPP), CupBF and OPP, and RimBF and OPP before (left) and after (right) the administration of timolol.
after 6-month treatment with dorzolamide or timolol indicated that autoregulation in our study population was close to the values we have reported in healthy subjects.8,19

A number of previous studies involving smaller study populations have also addressed this topic. Using single-point laser Doppler flowmetry, Gruenwald et al.20 reported that patients with glaucoma without systemic hypertension have lower optic nerve blood flow than those with hypertension.20 Most of these patients were receiving topical medication, and all had adequately controlled IOPs. In patients with progressive primary open-angle glaucoma with controlled IOP, a correlation between end diastolic blood velocities and systemic blood pressure was found. This association was, however, absent in patients whose conditions were stable and in healthy control subjects.21 Another study reported that arteriovenous passage times were significantly correlated with MAP and with mean and diastolic ocular perfusion pressure in patients with normal tension glaucoma, but not in healthy control subjects.22

How can these data of the present study be interpreted? Obviously, the result is not related to a direct vasodilator effect because such an effect was seen only with the carbonic anhydrase inhibitor and not with the beta receptor antagonist. An explanation may, however, be related to the complex mechanisms involved in the autoregulation of blood flow in the eye. In the rabbit, Kiel23–25 has intensively studied choroidal blood flow regulation during combined changes in arterial pressure and IOP. The latter can be seen as a direct manipulation of venous pressure because the IOP almost equals pressure of the vortex vein before it exits the sclera over a wide range of pressures.26 When IOP was held constant, Kiel23–25 noted that the degree of autoregulation in response to changes in arterial perfusion pressure was dependent on the absolute level of IOP. Autoregulation became less efficient when IOP was increased from 5 mm Hg to 25 mm Hg. The author speculated that this result was attributed to a myogenic mechanism underlying choroidal autoregulation. This hypothesis is in accordance with results we obtained in healthy subjects during combined increases in blood pressure induced by squatting and increases in IOP induced by suction cup.27 In these experiments choroidal blood flow was again better regulated during an exercise-induced increase in perfusion pressure than during a decrease in ocular perfusion pressure induced by experimental IOP increase. Regardless if present in a patient with glaucoma or ocular hypertension or in a healthy subject with experimentally induced IOP, an increase in IOP is associated with a decrease in ocular perfusion pressure and with an increase in the transmural pressure gradient. The myogenic theory assumes that changes in transmural pressure are responsible for smooth muscle relaxation in response to a decrease in perfusion pressure. Hence, normalization of IOP achieved by topical antiglaucoma medication may normalize the transmural pressure gradient toward normal, thereby normalizing blood flow regulation.

A limitation of the present study was that evidence of abnormal autoregulation and its normalization after IOP reduction arises from group correlations only. Additional studies investigating autoregulatory capacity during an experimental change in perfusion pressure before and after therapeutic IOP reduction are required. Such experiments are, however, difficult to perform because inducing experimental changes in perfusion pressure with concomitant measurements in blood flow are difficult to perform in patients with glaucoma. Another limitation of the present study was that a washout period of only 2 weeks was scheduled for previous antiglaucoma medications. Whether this was sufficient to exclude all ocular vasoactive effects of previous medications is unclear. Because the study was double masked and randomized, this was unlikely to have affected the conclusions of the present study.

In our previous paper, we reported that a tendency toward a reduction in systemic blood pressure was seen with both timolol and dorzolamide.3 This may be a consequence either of systemic absorption of the study drugs or of a reduction in the “consultation blood pressure” effect because patients became adapted to the study settings. This effect may influence the pressure/flow relationships reported in this article, but the decrease in blood pressure was small and not significant.

In addition, it must be considered that neither of the two methods measures blood flow in absolute units. With laser interferometry, only the pulsatile component of blood flow is assessed.17,18 Whether this is representative of total choroidal blood flow is unclear. Because the ocular hemodynamic effects of topical timolol and dorzolamide in the present study were small,2 however, it was unlikely that the treatment altered the ratio between pulsatile and nonpulsatile blood flow to a significant degree. With scanning laser Doppler flowmetry, several groups have raised concerns over the validity of the technique. Most important, Yu et al.28 have shown that in the rat, the signal arising from retinal capillaries is not altered when the central retinal artery is occluded. We have, therefore, concluded that the technique is not capable of measuring microvascular flow at the posterior pole of the eye. Moreover, it has been shown that measurements with scanning laser Doppler flowmetry are limited because of a large zero offset, which cannot be determined in vivo (Van Heuven WJ, et al. IOVS 1996;37:ARVO Abstract 4242). On the other hand, we have previously shown in a double-masked study design in healthy subjects that the technique is capable of detecting ocular hemodynamic changes during the inhalation of different gas mixtures of oxygen and nitrogen.14 Although this does not necessarily mean the relation between flow values measured with scanning laser Doppler flowmetry and actual blood flow values is linear, it indicates that the system can detect changes in blood flow. This is also supported by the results of the present study, in which a correlation between scanning laser Doppler flowmetry readings and systemic blood pressure was found. In interpreting these correlations, it must be considered that the technique does not measure blood flow in absolute units and that the relation between actual blood flow and scanning laser Doppler flowmetry readings is not linear. With measurements in the cup, it is not entirely clear which capillaries contribute to the signal. It is, however, unlikely that the signal is influenced by larger vessels in deeper layers because larger flow readings would be expected.

In conclusion, our data indicate that a reduction in IOP with either dorzolamide or timolol normalizes the pressure/flow relationship in patients with glaucoma or ocular hypertension. This effect is seen despite the fact that only dorzolamide, but not timolol, increased blood flow and therefore appears to be independent of a vasodilator effect. Whether this effect is related to the beneficial actions of IOP reduction in terms of visual field preservation must be established.

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