

Evaluation of retinal haemodynamics and retinal function after application of dorzolamide, timolol and latanoprost in newly diagnosed open-angle glaucoma patients

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ABSTRACT.

Purpose: The purpose of this prospective, randomized, cross-over study was to investigate and compare the microcirculatory effects of timolol, dorzolamide and latanoprost in newly diagnosed primary open-angle glaucoma (POAG) patients. Haemodynamics were assessed using fluorescein angiography by means of a scanning laser ophthalmoscope (SLO). Visual function and visual field indices were evaluated during all drug treatment phases.

Methods: Fourteen patients with newly diagnosed POAG (age 55 ± 7 years; 10 male, four female) were recruited for the study. At baseline examination, blood pressure, heart rate, intraocular pressure (IOP), SLO angiograms, and contrast sensitivity (CS) were analysed. Patients then randomly received timolol, dorzolamide or latanoprost treatment for 4 weeks. Patients then returned and all procedures were repeated and assessed. Arteriovenous passage times (AVPs), peripapillary arterial and venous diameters were assessed from SLO angiograms, using digital image processing. Calculated ocular perfusion pressure was determined for each treatment phase.

Results: Intraocular pressure was significantly lowered by each drug compared to baseline ($p < 0.0001$). Arteriovenous passage times were significantly shortened after dorzolamide application compared to baseline ($p = 0.009$), whereas neither timolol nor latanoprost treatment resulted in significant AVP changes. Peripapillary arterial and venous diameters, systolic and diastolic blood pressure, heart rate and ocular perfusion pressures were not significantly altered during any treatment phase. Contrast sensitivity testing at 6 cycles/degree (c.p.d.) revealed a significant rise after dorzolamide compared to timolol ($p = 0.007$).

Conclusion: Our results suggest that dorzolamide treatment significantly shortened AVP times in newly diagnosed open-angle glaucoma patients, whereas timolol and latanoprost had no significant effect. Given that prolonged AVP times have been associated with disease progression in glaucoma; dorzolamide treatment may benefit optic nervehead preservation by increasing ocular perfusion.

Key words: glaucoma – microcirculation – fluorescein angiography – dorzolamide – latanoprost – timolol

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Introduction

While reduction of intraocular pressure (IOP) represents the mainstay of medical therapy for glaucoma, other ocular effects of topical medications remain important. Reduced blood flow in the large ocular arteries and in the microcirculation of the optic nervehead has been observed in primary open-angle glaucoma (POAG) and normal tension glaucoma (NTG) (Harris et al. 1994; Rankin et al. 1995; Grunwald et al. 1998). Because there is accumulating evidence that vascular insufficiency or vasospasm may be associated with glaucomatous optic nervehead erosion in certain patients, it is of clinical interest that ocular medications such as dorzolamide, latanoprost and timolol be evaluated for their haemodynamic effects (Carter et al. 1990).

Latanoprost is a prostaglandin F_2 alpha analogue (13, 14-dihydro-17-phenyl-18, 19, 20-trinor-prostaglandin $F_{2\alpha}$ -isopropyl-ester) (Hejkal & Camras 1999). Based on physiological data, this drug may have a variety of vascular effects depending on the concentration and the exposed vascular bed (Stjernschantz et al. 1989).

Timolol 0.5% is a topical beta-blocker that has been widely used alone and in combination with other topical medications to lower IOP (Zimmermann & Boger 1979).

Dorzolamide hydrochloride is a potent inhibitor of human carbonic anhydrase (CA) isoenzymes II and IV. The inhibition of CA therefore decreases the rate of aqueous humour secretion, consequently lowering IOP. Preliminary evidence suggests that dorzolamide can improve central visual function in normal individuals when that function is measured during hyper- or hypocapnia (Harris et al. 1996). Improvements have been demonstrated in contrast sensitivity at both 3 and 6 cycles/degree (c.p.d.) in NTG patients without altering levels of pressure (P) CO_2 (Harris et al. 1999).

The causal factors for glaucoma are various and complex, and may include circulatory deficits as well as elevated

IOP (Hayreh et al. 1970). As the technology for measuring ocular blood flow continues to develop and improve, it is important to understand the ocular haemodynamic effects of glaucomatous medications. This study investigates the effects of latanoprost, dorzolamide and timolol on ocular haemodynamics and visual function in newly diagnosed POAG patients.

Material and Methods

Patients

Fourteen newly diagnosed POAG patients (age 55 ± 7 years; 10 male, four female) completed this prospective, randomized, cross-over study. Newly diagnosed POAG status was based on normal gonioscopy readings with repeated IOP measurements above 21 mmHg. Cup-to-disc ratios ranged from 0.2 to 0.8 (horizontal 0.46 ± 0.24 ; vertical 0.45 ± 0.24). Glaucomatous visual field loss was defined on the basis of Humphrey 24–2 full-threshold visual field examination. A glaucomatous field (European Glaucoma Society 1998) was considered in the absence of retinal or neurological disease, when one of the following three criteria was confirmed on two consecutive visits: abnormal glaucoma hemifield test; three points confirmed with $p < 5\%$ probability of being normal, one of which should have $p < 1\%$ and none of which should be contiguous with the blind spot, or corrected pattern standard deviation (CPSD) $< 5\%$ when the visual field was otherwise normal. Patients with myopia greater than -8.0 dioptres, a history of fluorescein allergy, diabetes mellitus, any vascular disorder or dense lens opacities precluding detailed fundus visualization were excluded.

Detailed explanations of all procedures were provided and informed consent was obtained from each subject prior to participation in the study. The protocol for the study was reviewed and approved by the Institutional Review Board of the Medical School

of the Technical University of Aachen. The tenets of the Helsinki Declaration were followed throughout the study.

The baseline examination included tests of blood pressure (BP), heart rate, IOP, scanning laser ophthalmoscope (SLO) angiograms, visual acuity (VA) and contrast sensitivity (CS). Patients were then randomized to receive timolol (twice daily; Chibro Timolol 0.5; Chibret, Munich, Germany) or dorzolamide (three times daily; Trusopt; Chibret, Munich, Germany) or latanoprost (once in the evening; Xalatan; Pharmacia, Erlangen, Germany) treatment for 4 weeks. At the end of the 4-week period, all measurements were performed again and thereafter the patients were started on the next drug for the following 4 weeks. The design and randomized order of medications were intended to establish a sufficient washout period of the anti-glaucomatous drugs before the following examination.

Methods

Digital scanning laser fluorescein angiography (Rodentstock Instruments, Ottonbrunn, Germany) was performed to assess retinal arteriovenous passage time (AVP). The methodology has been presented in detail elsewhere (Wolf et al. 1989a; Arend et al. 1999). Fluorescein intensity curves were registered using a frame grabber (Matrox Frame Grabber, Matrox Inc., Quebec, Canada) and the first entry of fluorescein in the retinal vessels was detected (Arend et al. 1999). The AVP time characterizes the passage from the retinal artery through the capillary formation and arrival in the vein and is correlated with macular capillary blood velocity (Arend et al. 1999).

The diameters of the temporal superior and inferior vessels at the site of measurement of AVP were assessed from the mid-transit fluorescein angiograms. A density profile was performed perpendicular to the vessel and by identifying the half height from the maximum height of the ascending and the descending slope diameter measurements (Delori et al. 1988; Arend et al. 2000). To reach subpixel accuracy, the measurement was performed five times and averaged. Mean AVP times and vessel diameters from the superior and inferior temporal vessel formations were analysed to characterize the posterior pole circulation.

Visual fields were taken on the same day as and prior to angiography. Visual fields were performed with a Humphrey Field Analyser (Humphrey Inc., San Leandro, California, USA) (program 24-2, full threshold, conventional full threshold white-on-white), using short wavelength automated perimetry (SWAP) (Johnson 2001). Global indices were analysed to match the criteria of glaucoma diagnosis.

Best-corrected visual acuity was tested using objective refractometry. Static contrast sensitivity (CSV 1000; Vector Vision, Dayton, Ohio, USA) was performed on all subjects at four spatial frequencies (3, 6, 12 and 18 c.p.d.) according to conditions described previously (Pomerance & Evans 1994).

Intraocular pressure was measured before angiography examination using Goldmann applanation tonometry. Heart rate and BP were determined using an automatic sphygmomanometry device (Vital Daten Monitor; Criticon Inc, Tampa, Florida, USA). All morphological measures were corrected for individual refractive error by using the ultrasonic A-scan length for calculation of Littmann factors (Littmann 1988; Bennett et al. 1994). Ophthalmic perfusion pressures were calculated from the BP and IOP data (perfusion pressure = 0.22 (systolic BP + 2 diastolic BP) – IOP).

Statistical analysis

Mean values and standard deviations were analysed for all samples using normal distributions (Kolmogorov–Smirnov test). For multiple comparisons, ANOVA for repeated measurements was used and p-values were obtained using Bonferroni–Dunn post hoc tests.

Results

Intraocular pressure was significantly lowered by each drug compared to baseline ($p < 0.0001$), but no differences were detected between groups (Table 1). Blood pressures, heart rates and calculated perfusion pressures showed no significant differences between visits (Table 1).

Retinal AVP times were significantly shortened after dorzolamide application compared to baseline examination ($p = 0.009$). Neither timolol nor latanoprost resulted in any significant retinal AVP time changes (Fig. 1, Table 2). No

Table 1. Data for systolic and diastolic blood pressure and heart rate (mean \pm SD). No significant differences between groups were detected for systolic blood pressure, diastolic blood pressure, heart rate and perfusion pressure (PP). Each treatment group differed significantly for IOP readings compared with baseline examination ($p < 0.0001$); however, no significant differences between groups were found.

| | Baseline | Timolol | Dorzolamide | Latanoprost | Significance* |
|------------------------|----------------|------------------|------------------|------------------|---------------|
| Systolic BP (mmHg) | 141 \pm 18 | 135 \pm 17 | 132 \pm 22 | 132 \pm 22 | NS |
| Diastolic BP (mmHg) | 88 \pm 12 | 82 \pm 8 | 84 \pm 10 | 82 \pm 10 | NS |
| Heart rate (beats/min) | 70 \pm 8 | 64 \pm 9 | 65 \pm 13 | 68 \pm 9 | NS |
| PP (mmHg) | 47 \pm 9 | 50 \pm 6 | 50 \pm 7 | 50 \pm 8 | NS |
| IOP (mmHg) | 22.2 \pm 3.6 | 15.7 \pm 3.2 † | 15.4 \pm 2.9 † | 15.2 \pm 2.6 † | $p < 0.0001$ |

* ANOVA repeated measures; NS = not significant.

† Bonferroni–Dunn post hoc test ($p < 0.0001$).

significant differences were detected among treatment options. Peripapillary arterial (Fig. 2, Table 2) and venous (Fig. 3, Table 2) diameters were unaffected during all antiglaucomatous medication treatment.

Contrast sensitivity testing revealed no significant differences between baseline readings and those taken after drug therapy at 6 c.p.d. However, a significant improvement at 6 c.p.d. was detected for dorzolamide compared to timolol ($p = 0.003$), whereas none of the other drug options differed from one another. Contrast sensitivity at other spatial frequencies showed no significant change (Table 3).

Discussion

Technological developments over the past two decades have led to a variety

of non-invasive and minimally invasive methods acceptable for *in vivo* use in humans. This has resulted in an increasing number of blood flow studies in clinical and experimental ophthalmic literature.

Drugs used to treat glaucoma lower IOP, thereby increasing ocular perfusion pressure; however, their net effect on vascular tone remains unclear. Although visual function stabilization can be expected with the use of antiglaucoma medications, visual benefit may be impaired due to ischaemic insult (Harris et al. 1999). Antiglaucoma drugs may have direct pharmacological effects on vessel calibre, which may either complicate or improve compromised ocular circulation. The vasoconstrictive properties of any drug may produce a negative impact on previously ischaemic retinal tissue. Thus it remains unclear, yet important,

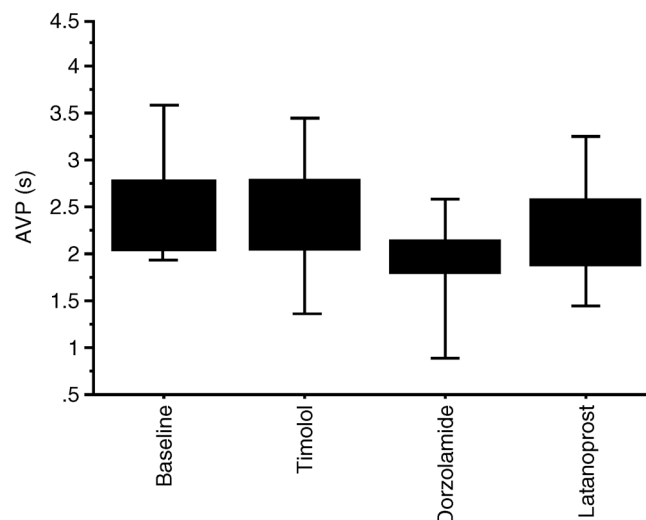


Fig. 1. Box plots displaying the 5%, 25%, 50%, 75% and 95% percentiles of the arteriovenous passage time (AVP) at baseline and after timolol, dorzolamide and latanoprost treatment. After dorzolamide application a significant reduction ($p = 0.009$; ANOVA) in AVP was observed compared to baseline examination.

Table 2. Data for arteriovenous passage time (AVP) arterial and venous diameters (mean \pm SD). After dorzolamide application a significant shortening in AVP was observed. Neither arterial nor venous diameters changed significantly.

| | Baseline | Timolol | Dorzolamide | Latanoprost | Significance* |
|------------------------------|-----------------|-----------------|-------------------|-----------------|---------------|
| AVP (seconds) | 2.53 \pm 0.72 | 2.35 \pm 0.85 | 1.94 \pm 0.58 † | 2.33 \pm 0.75 | p = 0.007 |
| Arterial diameter (μ m) | 96.1 \pm 11 | 95.5 \pm 12 | 93.4 \pm 13 | 92.8 \pm 8 | NS |
| Venous diameter (μ m) | 144.3 \pm 12 | 136.8 \pm 10 | 140.3 \pm 17 | 138.4 \pm 12 | NS |

* ANOVA repeated measures; NS = not significant.

† Bonferroni–Dunn post hoc test (p < 0.0009).

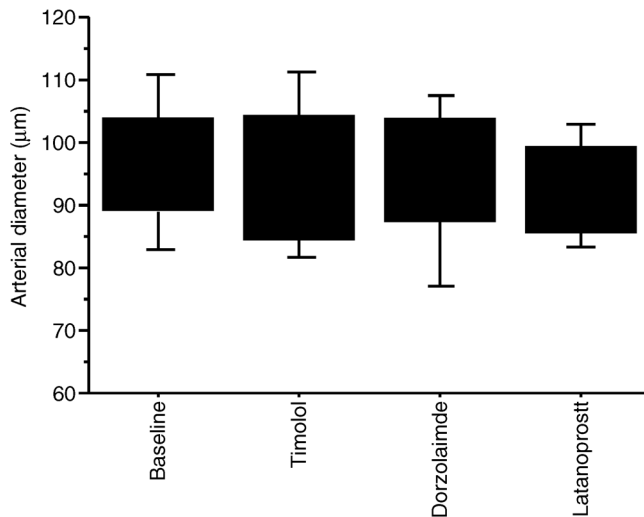


Fig. 2. Box plots displaying the 5%, 25%, 50%, 75% and 95% percentiles of the peripapillary arterial diameters at baseline and after application of timolol, dorzolamide and latanoprost. There were no statistical differences between groups (ANOVA).

what pressure-independent effects glaucomatous medications may have on ocular vasculature.

Latanoprost is a prostaglandin F₂ alpha analogue. Selective FP receptor

agonist activity is believed to reduce IOP by increasing the uveoscleral outflow of aqueous humour. The retinal vascular effects of latanoprost, however, remain unclear. Studies in animal

models have shown that prostaglandin F_{2α} causes both relaxation and constriction of ocular blood vessels (Denton et al. 1972; Uski & Andersson 1984; Kimura et al. 1992). Studies on choroidal circulation have shown an increased pulsatile ocular blood flow after instillation of latanoprost (Georgopoulos et al. 2002; Sponsel et al. 2002). Our research did not show any significant effects on retinal perfusion during latanoprost treatment.

Timolol had no significant effects on retinal AVP. Previous circulatory studies studying the effect of timolol remain controversial (Morsman et al. 1995; Harris & Martin 1997). Fluorescein angiographic studies showed shortened AVP time (Wolf et al. 1989b; Arend et al. 1998) and increased macular capillary blood red cell velocity (Arend et al. 1998) after acute application of timolol in healthy subjects. A 4-week application of betaxolol in NTG patients failed to show changes in AVP time (Harris et al. 2000). The differences between studies might be due to a short-term effect versus the longterm application of timolol. In the absence of beta-adrenergic receptors in the retina or the optic nervehead, no vasomotor effects were observed (Orgul et al. 1995; Arend et al. 1998). As previous studies suggest that timolol has minimal influence on retinal haemodynamics, our results are in agreement with current medical research findings (Morsman et al. 1995; Harris & Martin 1997).

The topical carbonic anhydrase inhibitor dorzolamide has been approved for chronic use in the treatment of glaucoma (Sugrue et al. 1997). The ocular hypotensive effects of this topical carbonic anhydrase inhibitor seem likely to produce the same results as beta-adrenergic antagonists (Sugrue et al. 1997). Systemic carbonic anhydrase inhibitors (CAIs) are known to have vasodilatory effects (Maren 1995). Rassam et al. (1993) concluded that acetazolamide, as a systemic CAI, causes an increase in retinal blood flow in the human retinal circulation. Previously, dorzolamide has demonstrated an ability to increase retinal circulation as measured by scanning laser ophthalmoscopy (Harris et al. 1996).

Dorzolamide has been shown to increase capillary flow velocity in the retina of NTG patients specifically (Harris et al. 1996). Reductions in the

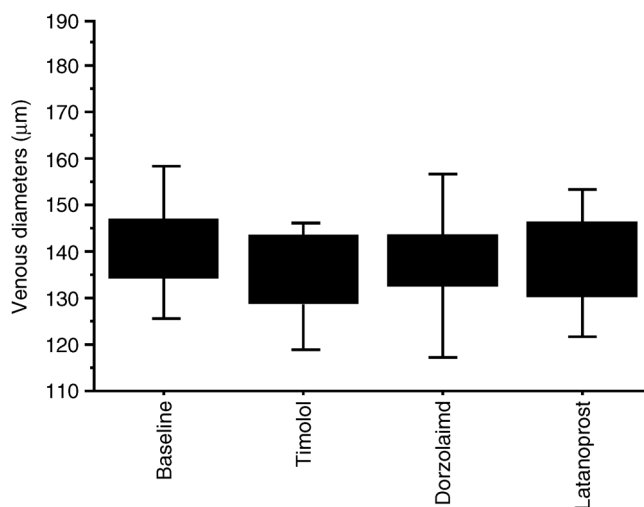


Fig. 3. Box plots displaying the 5%, 25%, 50%, 75% and 95% percentiles of the peripapillary venous diameters at baseline and after application of timolol, dorzolamide and latanoprost. There were no statistical differences between groups (ANOVA).

Table 3. Static contrast sensitivity results (mean \pm SD) for the four spatial frequencies (3, 6, 12, 18 c.p.d.). There were no statistical differences between groups (ANOVA) at 3, 12 and 18 c.p.d. At 6 c.p.d. significant differences between the dorzolamide and timolol groups ($p=0.003$) were detected.

| Contrast sensitivity | Baseline | Timolol | Dorzolamide | Latanoprost | Significance* |
|----------------------|-----------------|-----------------|------------------|-----------------|---------------|
| 3 c.p.d. | 1.68 \pm 0.27 | 1.57 \pm 0.22 | 1.68 \pm 0.16 | 1.72 \pm 0.13 | NS |
| 6 c.p.d. | 1.89 \pm 0.22 | 1.81 \pm 0.19 | 1.98 \pm 0.15† | 1.95 \pm 0.22 | $p=0.03$ |
| 12 c.p.d. | 1.41 \pm 0.24 | 1.46 \pm 0.29 | 1.58 \pm 0.24 | 1.52 \pm 0.27 | NS |
| 18 c.p.d. | 1.02 \pm 0.16 | 0.95 \pm 0.21 | 1.10 \pm 0.18 | 1.04 \pm 0.21 | NS |

*ANOVA repeated measures; NS = not significant.

†Bonferroni-Dunn post hoc test ($p < 0.007$).

AVP time of fluorescein dye coupled with rapid macular capillary transit time, when associated with unchanged retinal arterial and venous diameters, suggest that the medication enhances retinal perfusion.

In a study of healthy subjects, dorzolamide decreased AVP time and increased macular and superficial optic nervehead capillary transit velocities, without altering the diameter of the superior temporal artery or vein (Harris et al. 1996). Our study supports these findings with no influence of dorzolamide, timolol or latanoprost on the diameter of the superior or inferior temporal artery or vein. These results seem important with regard to experimentally induced vasoconstriction following prostaglandin $F_{2\alpha}$ application (Hoste 1997; Brogiolo et al. 2001). A vasoactive effect at the level of the capillary formation cannot be excluded and, in the absence of methodologies by which to examine these crucial diameters, results cannot be examined at present.

A 24% decrease in retinal AVP time after dorzolamide treatment was reported in glaucoma patients (Harris et al. 1996). Several other studies (Sponsel et al. 1997; Schmidt et al. 1998; Martinez et al. 1999; Stefánsson et al. 1999) have shown dorzolamide to have a vascular effect and therefore this drug might be beneficial in treatment in ophthalmic diseases, in which blood flow deficits have been implicated. In the current study, the results of shortened AVP times during dorzolamide treatment agree with those reported in previous studies on retinal circulation (Harris et al. 1996, 2000). In contrast, Bergstrand et al. (2002) showed unaffected AVP times in newly diagnosed and untreated POAG patients. The inconsistency of reported circulatory

results (Bergstrand et al. 2002) might be due to different study designs, ethnic populations and/or algorithms for analysis of the collected data. In addition to circulatory results, contrast sensitivity significantly improved for the medium spatial frequency range in accordance with previous reports (Sponsel et al. 1997; Harris et al. 1999).

The implications of these results remain unclear due to the small sample size. Previous angiographic studies have shown significant results detected in small samples (Harris et al. 1996, 1999, 2000; Arend et al. 1998, 2000). The non-significant effects on BP, heart rate and perfusion pressure could be due to a higher variability of these measures and the small sample size. Therefore, the systemic data have to be interpreted cautiously.

In conclusion, dorzolamide treatment significantly shortened retinal AVP times in newly diagnosed POAG patients. Contrast sensitivity also improved significantly with dorzolamide treatment at the medium spatial frequency range compared to timolol. Prolonged AVP times have been associated with disease progression in glaucoma (Arend et al. 2000). Increasing retinal blood flow to the ocular tissue beds may help visual function, as seen during CS testing at 6 c.p.d. The implications of the increased retinal perfusion arising from shortened AVP times remain unclear with regard to the overall picture of ocular blood flow.

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