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Comparative analysis of the effects of dorzolamide and latanoprost on ocular hemodynamics in normal tension glaucoma patients

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PURPOSE. *To compare the effects of latanoprost (Xalatan®) and dorzolamide (Trusopt®) on ocular hemodynamics in normal-tension glaucoma patients.*
METHODS. *A randomized, single-masked, parallel design study was conducted. After a 4 - week washout period, 20 normal tension glaucoma patients, recruited from a single university-based ophthalmology clinic, received either latanoprost once daily or dorzolamide 3 times daily for 4 weeks. The subjects were examined at baseline and post-treatment. Outcome measures included heart rate (HR), blood pressure (BP), logMar visual acuity (VA), contrast sensitivity (CS), intraocular pressure (IOP), color Doppler imaging (CDI), and fluorescein angiography with the Rodenstock scanning laser ophthalmoscope (SLO). CDI measurements of the retrobulbar vessels included peak systolic velocity, end diastolic velocity, and the calculated resistance index. Arterio-venous passage time (AVP) in the superior and inferior temporal retina was calculated from the SLO angiograms.*
RESULTS. *Neither dorzolamide nor latanoprost had any statistically significantly effect on HR or BP. Both drugs significantly lowered IOP without altering calculated ocular perfusion pressure ($p<0.05$). There was no statistically significant difference in any CDI measurement. Dorzolamide significantly decreased AVP time in the superior retina ($p=0.011$), while latanoprost did not ($p=0.62$).*
CONCLUSIONS. *Dorzolamide, unlike latanoprost, significantly reduced AVP times in the superior temporal retina in normal tension glaucoma (NTG) patients. (Eur J Ophthalmol 2003; 13: 24-31)*

KEY WORDS. *Glaucoma, Hemodynamics, AVP time, Dorzolamide, Latanoprost*

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INTRODUCTION

Glaucoma is a progressive optic neuropathy involving characteristic structural changes of the optic nerve and characteristic visual field defects. Increased ocular pressure is the risk factor most often associated with glaucomatous optic neuropathy. However, the progression of glaucomatous damage in patients with lowered intraocular pressure (IOP) and normal tension glaucoma (NTG) suggests risk factors other than IOP (1-2). A recent study has shown additional risk factors exist for NTG progression, including the female gender, migraine, and disk hemorrhages (2). Furthermore, 20% of NTG patients continued to progress and not all untreated patients developed further damage (2). Studies have demonstrated that ocular blood flow plays a critical role in the clinical course of glaucoma (3-4). Additionally, reduced blood flow in large oc-

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ular arteries and in the microcirculation of the ocular nerve head (ONH) in primary open angle glaucoma (POAG) and in NTG has been observed (5-7). Several local vascular alterations such as ophthalmic artery stenosis, decreased blood flow velocity, increased resistance in the central retinal and short posterior ciliary arteries have been associated with both NTG and POAG patients (8). Even though the reduction of IOP is the traditionally acknowledged form of treatment for glaucoma we need to understand the effect of the IOP reducing medications on ocular blood flow.

Dorzolamide, a topical carbonic anhydrase inhibitor, has been approved for chronic use in the treatment of glaucoma. The ocular hypotensive effects of dorzolamide are similar to β-adrenergic antagonists (9). Systemic carbonic anhydrase inhibitors are known to have vasodilatory effects and to increase retinal blood flow (10-11). Barnes et al showed a significant increase in optic nerve perfusion in rabbits after a week of dorzolamide treatment (12). Dorzolamide has also been shown to significantly increase pulsatile ocular blood flow (POBF) in glaucoma patients (13,14). In previous studies, we found that dorzolamide increases the retinal circulation through a decrease in the retinal arteriovenous passage time (AVP) as measured by scanning laser ophthalmoscopy fluorescein angiography (SLO) (15-18).

Latanoprost, a prostaglandin $PGF_{2\alpha}$ analogue, effectively reduces IOP in normal and glaucomatous eyes by increasing the outflow of aqueous humour (19,20). This effect is likely mediated through its selective FP receptor agent activity. The $PGF_{2\alpha}$ has been shown to either constrict or relax vascular smooth muscle (21, 22). Some studies have shown $PGF_{2\alpha}$ to induce constriction in bovine retinal arteries and cat ophthalmociliary arteries (23, 24), yet it has no effect on regional blood flow in the monkey eye (25). The effects of latanoprost on human ocular circulation has been studied by a number of methods resulting in different findings. Nicolela et al (26) did not observe any change in blood velocity in the retrobulbar arteries, using CDI, after latanoprost application in glaucoma and ocular hypertensive patients. Additionally, a Heidelberg retinal flowmetry (HRF) study in healthy subjects demonstrated no significant change in the peripapillary retinal blood flow one-day post latanoprost administration (27). Martinez et al, however, found significantly increased EDV and decreased RI in the OA and CRA in normal tension glaucoma and healthy subjects (28). Recent papers report a significant increase in POBF in normal subjects (29,30). Sponsel et al observed significant increases in POBF and HRF flow after one week of topical therapy with latanoprost (31). Vetrugno et al showed a 56% increase in POBF after one day of latanoprost application, with this increase remaining at 23% after 180 days of treatment (32). McKibben and Menage found an increase of 21% in POBF after one month of latanoprost treatment in NTG (33). The present study evaluates the effects of latanoprost as compared to dorzolamide on ocular hemodynamics in normal tension glaucoma patients.

METHODS

Design

A randomized, single-masked, parallel study was employed. Each visit included vital signs (heart rate and blood pressure), visual acuity (VA), contrast sensitivity (CS), IOP and dilated fundus exam for both eyes. Vascular measurements including CDI and SLO with fluorescein angiography were conducted on a randomly chosen eye. All subjects were included after a 4-week drug washout period, and were randomly divided into two groups. The first group (n=10) received 2% dorzolamide three times daily, while the second group (n=10) received 0.005% latanoprost once daily for a total of four weeks. Measurements were performed at baseline (the end of the washout period) and after four weeks of treatment.

Setting

This study was conducted at the Glaucoma Research and Diagnostic Center, Indiana University School of Medicine.

Patient population

Normal-tension glaucoma patients (n=20) were defined on the basis of characteristic glaucomatous visual field loss, ONH damage, and IOP less than 21 mmHg on multiple measurements prior to study enrolment. Patients with a mean visual field deviation greater than or equal to 20 dB, as measured by the

Humphrey Visual Fields 24-2 [Humphrey Automated Threshold Perimeter STATPAC 24-2 program] or with a cup/disc ratio of 0.9 or greater, were not included in the study. Subjects were all over the age of 18 and were required to have a corrected visual acuity of 20/40 or better. In addition, nursing mothers and female patients of childbearing age who were planning to become pregnant within eight months after study completion were excluded. Subjects did not have any current or significant past history of respiratory diseases or ocular diseases other than glaucoma. All procedures conformed to the tenets of the declaration of Helsinki and were reviewed and approved by the Institutional Review Board, with subjects signing an informed consent.

Observation procedures

On each visit, heart rate (HR), blood pressure (BP), VA, CS and IOP by Goldmann applanation tonometry were measured. The ocular perfusion pressure (PP) of each patient was calculated using the equation:

$$PP = (2/3 \cdot \text{mean arterial BP}) - IOP$$

Blood velocity was assessed using CDI, an ultrasound technique that combines B-scan grey scale imaging of tissue structure, colored representation of blood flow based on Doppler shifted frequencies, and pulsed-Doppler measurement of blood flow velocities. Blood flow velocities were assessed in the ophthalmic (OA), central retinal (CRA), and posterior (nasal and temporal) ciliary arteries (NPCA and TPCA, respectively). The Siemens Quantum 2000 colour Doppler imaging system (Siemens Quantum, Inc., Issaquah, WA) with a 7.5 Mhz linear probe was used to perform all measurements. This system analyses a sample of pulsed-Doppler signal from a small sample volume (0.2 mm x 0.2 mm) to calculate blood flow velocities.

During the test, subjects were reclined in a chair to about 60 degrees. Acoustic coupling gel was then placed over the closed eye and the probe was gently positioned. As little pressure as possible was applied during the test. After identification of the appropriate vessel, the angle of incidence was selected and several seconds of Doppler waveform were recorded. The peak and trough of the frequency waveform were selected by the operator and the instrument then calculates PSV, EDV, and RI (Pourcelot's resistance index). RI, measure of peripheral vascular resistance, was calculated for each vessel. RI is calculated by

$$RI = (PSV - EDV) / PSV$$

The test/retest reproducibility of this technique has been described previously (34).

Fluorescein angiography with the Rodenstock scanning laser ophthalmoscope (SLO 101, Ottobrun Germany) was utilized to evaluate ocular hemodynamics. This study was conducted 20 minutes after dilation with 0.1% tropicanimide and involved the use of a low powered laser to illuminate the inner eye. To perform the angiography, a 5cc injection of sodium fluorescein 10% dye was given as a single bolus into a cubital vein followed by a saline flush. With the scanning laser focused on the ONH and using a 20º image, the appearance of the dye passing through the capillaries in the region of the ONH was recorded on videotape. Throughout the test, patient fixation was controlled by simple verbal instruction. Six 5X5 pixel areas were selected for measurement. Two each on superior and inferior temporal arteries were chosen and one each on superior and inferior temporal veins. The AVP time is defined as the interval between the first influx of dye into the retinal artery and its first appearance in the corresponding retinal vein. It is the shortest circulation time of the indicator through a corresponding area of retinal microcirculation. The measurement is carried out by focusing one measuring area on an artery and a second one on the corresponding vein. The arterial measuring area is focused on the center of the vessel. The venous area is focused on both the center of the vessel and border where the first laminar filling can be seen. Both areas are positioned near the rim of the optic nerve. The time difference between the first rise of intensity in the artery and the first rise in the corresponding vein represents the AVP time (35,36).

Main outcome measures

Descriptive statistics were obtained for each baseline and treatment measurement. A Masters level biostatistician was consulted for analysis of the data. Pre- and post-medication hemodynamic parameters

were compared by a nonparameteric paired Wilcoxon signed ranked test. The unpaired non-parametric Mann-Whitney U test was used to compare all parameters between group 1 and group 2 at baseline and after treatment with their respective drug.

RESULTS

Neither dorzolamide nor latanoprost had any statistically significant effect on HR and BP (Tab. I). While both drugs significantly reduced IOP levels (Fig. 1), neither drug had a statistically significant effect on the calculated PP.

CDI demonstrated no statistical difference in the OA, CRA or PCA's for any parameter between baseline and post-drug for either drugs (Tab. II). Additionally, there was no statistically significant effect seen on the calculated RI. The SLO analysis showed no difference in AVP time in either the superior or inferior temporal peripapillary area between the two groups at baseline. Dorzolamide significantly decreased AVP time in the superior temporal retina (p=0.011), while latanoprost did not (p=0.62) (Fig. 2). Additionally, the Mann Whitney U test showed the post-drug percent change in AVP times between group 1 and group 2 had a statistically significant difference in the superior temporal retina only (p = 0.036) (Fig. 3). Due to inadequate compliance of some patients, only 8 of the 10 SLO measurements for each group were able to be analysed.

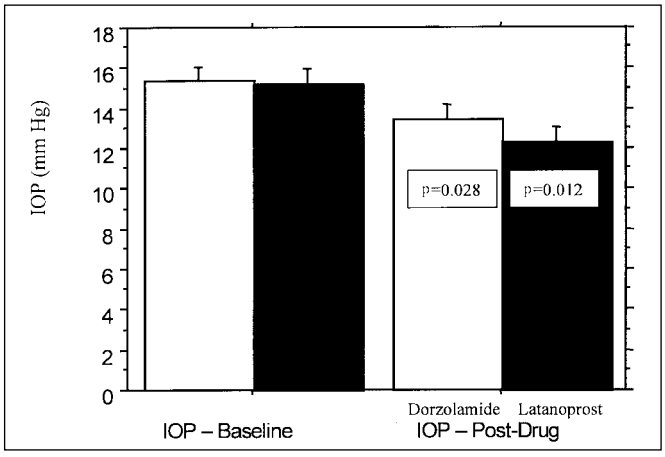

Fig. 1 - *IOP measurements (mmHg) at baseline and post-drug treatment. P values are the result of a Wilcoxon paired signed rank test. White bars represent the group randomized into dorzolamide treatment and black bars represent the group randomized into the latanoprost treatment.*

TABLE I - VISUAL ACUITY (VA), CONTRAST SENSITIVITY (CS), INTRAOCULAR PRESSURE (IOP), BLOOD PRESSURE (BP), HEART RATE (HR), AND PERFUSION PRESSURE (PP) (mean ± SD) AT BASELINE AND POST-DRUG TREATMENT

Parameters	Baseline	Dorzolamide	Baseline	Latanoprost
VA	0.026 ± 0.165	0.236 ± 0.4	0.062 ± 0.192	0.1 ± 0.124
CS				
3 cycles/degree	1.357 ± 0.522	1.463 ± 0.375	1.631 ± 0.268	1.580 ± 0.266
6 cycles/degree	1.733 ± 0.456	1.753 ± 0.225	1.745 ± 0.370	1.730 ± 0.363
12 cycles/degree	1.282 ± 0.462	1.310 ± 0.420	1.198 ± 0.421	1.419 ± 0.278
18 cycles/degree	0.854 ± 0.313	0.919 ± 0.383	0.747 ± 0.373	0.867 ± 0.294
IOP (mmHg)	15 ± 2	13 ± 2	15 ± 2	12 ± 2
Supine systolic BP (mmHg)	122 ± 18	122 ± 12	125 ± 20	119 ± 21
Supine diastolic BP (mmHg)	76 ± 12	72 ± 9	78 ± 12	73 ± 8
Supine HR (b.p.m.)	71 ± 12	73 ± 13	72 ± 10	72 ± 11
PP (mmHg)	45 ± 9	46 ± 6	48 ± 9	48 ± 7

Statistical significance of comparisons is provided in the text

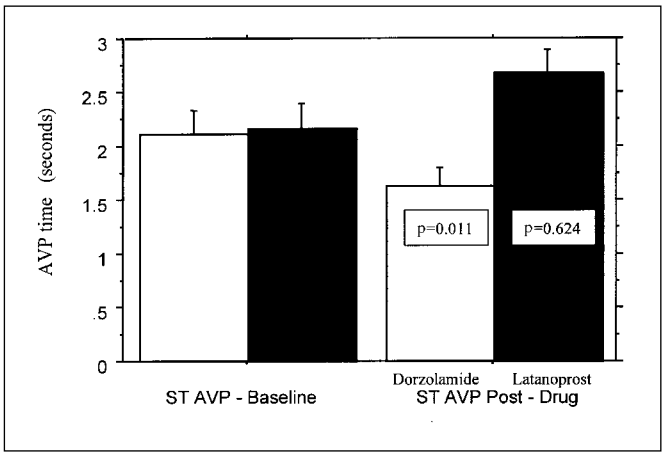

Fig. 2 - *A comparison of arterio-venous passage (AVP) times (seconds) in the superior temporal peripapillary retinal area (ST) at baseline and post-drug treatment. p values are the result of a Wilcoxon paired signed rank test. White bars represent the group randomized into dorzolamide treatment and black bars represent the group randomized into the latanoprost treatment.*

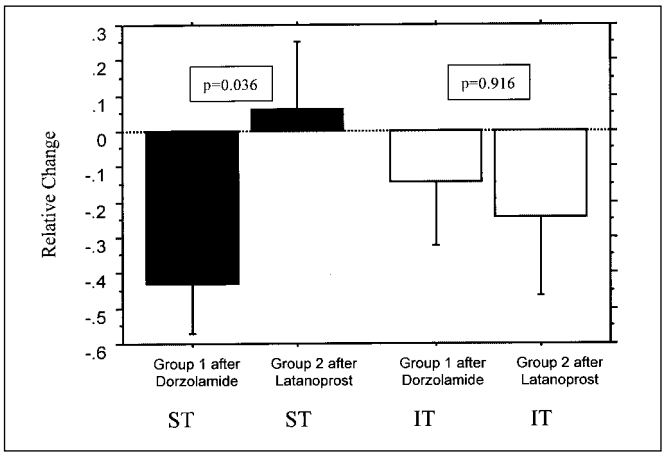

Fig. 3 - *A comparison between post-drug arterio-venous passage (AVP) times in the superior temporal (ST) and inferior temporal (IT) peripapillary retinal area. The p value above each set of data was generated using a Mann Whitney U test and represents whether a significance was seen between the two drug treatment groups.*

DISCUSSION

In this study, we found that dorzolamide and latanoprost had a similar hypotensive action in the eyes of patients with NTG. Both of these agents failed to alter retrobulbar flow velocities, as measured by CDI. These results are similar to those previously seen by our group (15-17, 37, 38). Using CDI, Nicolela et al did not observe any change in blood velocity in ocular vessels after latanoprost application in glaucoma and ocular hypertensive patients (26). These failures to detect changes in blood velocities with both latanoprost and

TABLE II - VELOCITY AND RESISTIVE INDEX MEASURES IN THE FOUR EXAMINED ORBITAL ARTERIES AS MEASURED BY COLOR DOPPLER IMAGING (CDI) (mean + SD)

Parameters	Baseline	Dorzolamide	Baseline	Latanoprost
OA				
PSV (cm/s)	31.704 ± 6.725	29.070 ± 7.300	27.323 ± 9.627	28.206 ± 9.372
EDV (cm/s)	7.310 ± 1.871	7.506 ± 2.142	6.636 ± 2.313	6.794 ± 2.828
RI	0.762 ± 0.073	0.731 ± 0.070	0.748 ± 0.050	0.762 ± 0.058
CRA				
PSV (cm/s)	8.199 ± 2.072	7.269 ± 1.720	7.305 ± 1.568	7.527 ± 1.712
EDV (cm/s)	1.898 ± 0.740	1.781 ± 0.861	1.535 ± 0.374	1.569 ± 0.360
RI	0.771 ± 0.065	0.755 ± 0.090	0.787 ± 0.041	0.785 ± 0.048
NPCA				
PSV (cm/s)	6.056 ± 1.467	6.322 ± 1.247	5.916± 1.192	5.918 ± 1.116
EDV (cm/s)	1.768 ± 0.401	1.834 ± 0.663	1.559 ± 0.306	1.582 ± 0.269
RI	0.699 ± 0.075	0.712 ± 0.084	0.733 ± 0.049	0.730 ± 0.035
TPCA				
PSV (cm/s)	7.365 ± 1.859	6.846 ± 1.544	6.547 ± 1.334	6.173 ± 1.255
EDV (cm/s)	2.042 ± 0.746	1.861 ± 0.743	1.606 ± 0.303	1.570 ± 0.218
RI	0.721 ± 0.084	0.723 ± 0.110	0.749 ± 0.045	0.740 ± 0.048

Statistical significance of comparisons is provided in the text
OA= Ophthalmic; CRA= Central retinal; NPCA= nasal posterior ciliary arteries; TPCA= tempotal posterior ciliary arteries

dorzolamide, using CDI, may be due to the limited number of subjects included in the studies. In fact, using CDI, Martinez et al previously found significantly increased EDV and decreased RI in the OA and CRA in a larger number of normal tension glaucoma and healthy subjects after dorzolamide treatment (28). Studies with larger populations, such as Martinez et al, need to be conducted in order to evaluate the minute effect of these drugs on ocular blood velocities with higher statistical power and greater sensitivity.

Dorzolamide, unlike latanoprost, significantly reduced AVP times in the superior temporal retina. The AVP time is a measurement of the time required for blood to pass from the arterial to venous system in the retina, therefore, a decrease in AVP time may suggest an increase in blood velocity, and possibly blood flow. However, this decrease could also be the result of a capillary de-recruitment. PP did not increase despite the lowering effect on IOP by both drugs. It is likely that this effect is unrelated to mechanical changes with the drug and related more to the pharmacological effects of dorzolamide on the retina. Considering that the drugs had a similar hypotensive effect, yet different vascular effects, provides further evidence to support a local vasoactive as opposed to an ocular-tension mechanism.

We have shown that dorzolamide effects only the retinal vascular bed, and not retrobulbar vessels. Previously, we demonstrated no change in OA velocity, despite substantial dosages of systemic carbonic anhydrase inhibitors (38). Considering that the present study was conducted using topical application of dorzolamide, there is a possibility that the drug could be reaching the posterior pole without reaching the retrobulbar vessels. Alternatively, the concentration of dorzolamide necessary to induce changes in the larger retrobulbar vessels is greater than that required to effect the retinal circulation.

Our findings of a regionally different affect is supported by other studies that have shown a different vasoactive response between superior and inferior retinal vasculature, as well as anatomical differences (39,40). In a previous study by our group, dorzolamide was found to decrease AVP time in NTG patients in the inferior temporal retina ($p=0.04$) without a statistically significant decrease in the superior temporal area ($p=0.12$) (17). These results are different from the ones in the current study. Possible explanations for these differences may be the different baseline AVPs between the two studies. For example, a superior temporal baseline AVP of 3.13 seconds in the previous study versus 2.12 seconds in the current one. Other possible explanations could be the different visual field defects, different baseline IOP (Near 17 mmHg in the previous study versus 15 mmHg in the current one) or demographic differences between the subjects in the two studies. We can accept this difference considering the physiologic mechanism underlying the vasoactive effects of dorzolamide on different vascular beds is unknown. Additionally, this suggests that dorzolamide has differing vascular effects which are dependent on the patient population and/or the progression and characteristics of the disease. However, because multiple studies have shown a positive vascular effect with dorzolamide, we conclude that this drug may be most beneficial in conditions similar to NTG, in which vascular dysregulation may play an important role.

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