The Effect of Brimonidine Tartrate on Retinal Blood Flow in Patients With Ocular Hypertension

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• PURPOSE: To study the effects of topical brimonidine tartrate 0.2%, an α_2-agonist ocular hypotensive drug, on retinal capillary blood flow in patients with ocular hypertension.

• METHODS: The study was a double-masked, randomized, placebo-controlled trial set in a tertiary eye center. Ocular hypertensive patients with repeatable intraocular pressures greater than 21 mm Hg and normal visual fields and optic disks were consecutively recruited. After an eye examination, baseline retinal blood flow measurements were made with confocal scanning laser Doppler flowmetry in one study eye. Patients were then randomly assigned to receive either brimonidine or placebo (saline) twice daily for 8 weeks. Blood flow and intraocular pressure measurements were then repeated after 4 and 8 weeks.

• RESULTS: Seventeen patients were randomly assigned to receive brimonidine, and 14 received placebo. One patient in each group failed to complete the study. The mean group differences in baseline age and intraocular pressure were not statistically significant (59.23 [±10.24] and 52.23 [±16.46] years, respectively, and 24.84 [±2.08] and 24.56 [±2.85] mm Hg, respectively). Brimonidine reduced intraocular pressure by 17.90% and 16.17% at 4 and 8 weeks, respectively, with a significant difference in treatment effect compared with the placebo group ($P < .007$). The group difference in treatment effect in any of the three hemodynamic parameters velocity, volume, and flow was within 8% and not significantly different at 4 or 8 weeks ($P > .360$). Based on a type I error of 0.05, our study had a power greater than or equal to 75% to detect group differences in treatment effect of greater than or equal to 15% to 20%.

• CONCLUSIONS: Brimonidine reduces intraocular pressure without altering retinal capillary blood flow in patients with ocular hypertension. (Am J Ophthalmol 2000;129:297–301. © 2000 by Elsevier Science Inc. All rights reserved.)

Accepted for publication June 9, 1999.

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This study was supported by the MacKeen Studentship from the Dalhousie Medical Research Foundation, Halifax, Nova Scotia, Canada (Mr Carlsson), and by a grant from Allergan Pharmaceuticals, Irvine, California (Dr Chauhan).

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BRIMONIDINE TARTRATE IS AN α_2-AGONIST OCULAR hypotensive drug that exerts its effect by causing both a decrease in aqueous production and an increase in uveoscleral outflow.[1] It is relatively new and has been proven to reduce increased intraocular pressures in glaucoma and ocular hypertension.[2,3] As an α_2- agonist, brimonidine belongs to the same class of drugs as clonidine and apraclonidine[4]; however, its molecular structure is sufficiently different to make it more selective for the α_2-receptor than either clonidine or apraclonidine. Unlike clonidine, brimonidine does not appear to have an effect on the central nervous system and therefore does not cause sedation or systemic hypotension.[5] Unlike apraclonidine, brimonidine causes less ocular irritation and allergy, probably because it has a lower oxidation potential than apraclonidine.[6,7] Brimonidine has few reported side effects, the most common being dry mouth.[2,3,7] Studies have also shown that brimonidine is free of any cardiopulmonary side effects that are associated with the β-blocking ocular hypotensive agents.[8,9]

Because brimonidine is an adrenergic agent, we wanted to determine whether topical application produced any significant effect on retinal microvascular blood flow.

PATIENTS AND METHODS

THIS STUDY WAS A SINGLE-CENTERED, DOUBLE-MASKED, randomized, placebo-controlled trial that determined the effect of brimonidine tartrate 0.2% on retinal capillary

blood flow in ocular hypertensive patients. Patients with increased intraocular pressure but normal visual fields and optic disks were recruited consecutively from the Eye Care Centre of the Queen Elizabeth II Health Sciences Centre, a tertiary care referral center. Informed consent was obtained from all patients. The study was approved by the Research Ethics Committee of the Queen Elizabeth II Health Sciences Centre.

Patients were included in the study if they had all of the following: best-corrected visual acuity of 20/30 or better; normal visual fields in both eyes with a mean deviation index of better than −2.00 dB and a normal Glaucoma Hemifield Test[10] using the STATPAC program for the Humphrey Field Analyzer (Humphrey Instruments, San Leandro, California); clinically normal funduscopic examination, including a normal-appearing optic disk; and documented intraocular pressure greater than 21 mm Hg on three separate occasions without treatment.

Patients were excluded if they had any of the following: diabetes; any disease known to affect blood flow, for example, polycythemia, temporal arteritis, and systemic vascular disease; use of oral calcium channel blockers, β-blockers, α-agonists, or angiotensin-converting enzyme inhibitors; refractive error greater than 6 diopters (spherical equivalent) or astigmatism greater than 2 diopters; aphakia or pseudophakia; and untreated intraocular pressure greater than 30 mm Hg.

Retinal blood flow was measured noninvasively using confocal scanning laser Doppler flowmetry,[11] a modification of the laser Doppler flowmetry technique described by Riva and associates.[12] The technique relies on measuring time-related intensity variations of backscattered light from an illuminated spot on the fundus. These intensity variations are the result of interference between backscattered light from stationary structures, such as tissue and vessel walls, and from moving blood particles. The intensity variation measurements are subjected to a fast Fourier transform to obtain the power spectrum of the multiple frequency shift components. Thereafter, three hemodynamic variables, velocity, volume, and flow, are computed from the power spectrum in arbitrary units.[13] Confocal scanning laser Doppler flowmetry was carried out using the Heidelberg Retina Flowmeter (Heidelberg Engineering GmbH, Heidelberg, Germany). The instrument and its operation have been detailed elsewhere.[14] Briefly, a diode laser (wavelength, 780 nm) is used to scan an area of 10.0 degrees by 2.5 degrees after it has been focused at the desired axial plane (for example, the retina). The image resolution is 256 by 64 picture elements (pixels). Each of the 64 horizontal lines is scanned 128 times, with a line repetition rate of 4 kHz over 2.05 seconds. The 128 intensity measurements at each location are made by a photodiode behind a confocal pinhole. The result of each processed scan is a two-dimensional perfusion map of the imaged area (Figure 1). The measurements derived with this technique have been shown to have good reproducibility[14–16] and to have a linear relationship to actual flow rates in an experimental model system.[17]

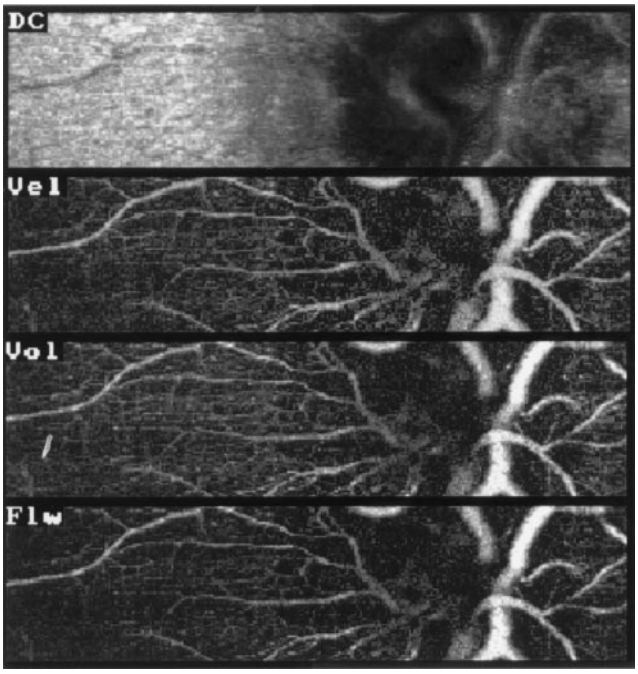

FIGURE 1. Confocal scanning laser Doppler flowmetry images obtained from a single scan of the temporal peripapillary retina of a subject in the study. (Top) Reflectivity image, akin to a funduscopic image and perfusion maps showing the (second) velocity, which is proportional to the mean Doppler shift; (third) volume, which is proportional to the concentration of particles moving through the sampling volume of tissue; and (bottom) flow, which is proportional to the blood flow through the sampling volume. The brightness of the pixels is scaled according to the respective hemodynamic values.

Patients who were receiving treatment for ocular hypertension underwent a 4-week washout period before enrollment. For safety purposes these patients had a full eye examination including intraocular pressure measurement halfway through the washout. At the baseline visit before randomization, patients underwent a full ophthalmic examination including visual acuity measurement, slit-lamp evaluation of the anterior segment, intraocular pressure measurement, and funduscopic examination of the retina and optic disk. Automated central visual fields were then recorded in both eyes with the 24-2 program of the Humphrey Field Analyzer to ensure eligibility. All patients were previously exposed to automated perimetry on several occasions. If both eyes were eligible for the study, one eye was randomly selected as the study eye. Confocal scanning laser Doppler flowmetry was then carried out in the study eye. Five good-quality images of the temporal retina, with a portion of the optic disk, were recorded. Patients were then randomly assigned to receive either brimonidine tartrate 0.2% (Alphagan; Allergan Pharmaceuticals, Irvine, California) or saline twice daily in the study eye. The

eye examination, tonometry, and flowmetry (with images recorded in the same retinal location as baseline) were repeated 4 and 8 weeks after baseline. The follow-up visits were scheduled at approximately the same time of day (within 1 hour) as baseline.

After the final visit we analyzed the flowmetry data in each scan by averaging the hemodynamic values in each of five 100 × 100-μm areas (each containing 100 individual measurements) in the temporal peripapillary retina. We ensured that measurements were made only in capillary beds and that for a given patient they were made in the same locations by using landmarks on the fundus reflectivity image (and not the perfusion maps), which is also provided in the analysis. We determined the session mean for each of the five 100 μm by 100 μm areas and after applying a log-transform determined the change in the hemodynamic parameters at the 4-week and 8-week points. After breaking the treatment code, we compared the treatment effect between the brimonidine and placebo group at the 4-week and 8-week points using a group *t* test. Intraocular pressure and age data were also compared using a group *t* test. We used group difference in treatment effect as the test statistic because it allowed control within subjects (treatment effect) and a direct comparison between the brimonidine and placebo groups (group *t* test).

RESULTS

THE STUDY HAD 14 PATIENTS IN THE BRIMONIDINE GROUP and 17 patients in the placebo group. One patient, randomly assigned to receive placebo, was withdrawn after 4 weeks, when her intraocular pressure exceeded 30 mm Hg. Another patient, randomly assigned to receive brimonidine, withdrew voluntarily in the sixth week of the study after developing dizziness and headaches. Thus, 13 patients in the brimonidine group and 16 patients in the placebo group completed the study.

The mean age (±1 SD) in the brimonidine and placebo groups was 59.23 (±10.24) and 52.23 (±16.46) years, respectively. The respective figures for baseline intraocular pressure were 24.84 (±2.08) and 24.56 (±2.85) mm Hg. The group difference in neither baseline age nor intraocular pressure was statistically significantly different ($P > .200$).

The intraocular pressure treatment effect between the brimonidine and placebo groups was significantly different at both the 4-week and 8-week points ($P < .007$, Figure 2), with the pressure reduction in the brimonidine group being 17.90% and 16.17%, respectively. The difference in treatment effect between the brimonidine and placebo groups was within 8% for each of the three blood-flow parameters analyzed at either the 4-week or 8-week points (Figure 3). These differences were not significantly different ($P > .360$). There was also no relationship between the change in intraocular pressure and change in blood flow in either the brimonidine or placebo group at the 4-week ($P > .790$) or 8-week ($P > .590$) points.

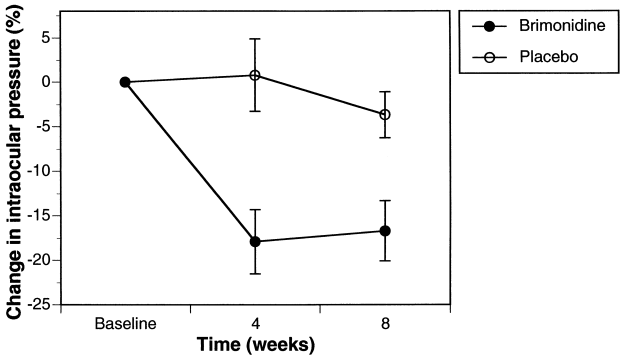

FIGURE 2. Change in intraocular pressure at the 4-week and 8-week points from baseline in the brimonidine and placebo groups (error bar = ±1 SE).

Based on the study sample size, we determined the statistical power to detect differences in treatment effect between the brimonidine and placebo groups. These calculations were done for 5%, 10%, 15%, 20%, 25%, and 30% group differences in treatment effect (Figure 4) and show that our study was adequately powered (greater than or equal to 75%, with type I error [α] = 0.05) to detect group differences of greater than or equal to 15% for the volume parameter and greater than or equal to 20% for the velocity and flow parameters.

DISCUSSION

PREVIOUS STUDIES HAVE SHOWN THAT α_2-ADRENORECEPTORS play an important role in microvascular autoregulation, particularly at the level of the terminal arteriole in vascular smooth muscle.[18–20] It is known that the retinal and optic nerve head microvascular network is under sensitive autoregulatory control,[21,22] and that α_2 binding sites are present in the retinal vasculature.[23] Spada and associates[24] studied the effect of various concentrations of brimonidine tartrate, an α_2-agonist, on human retinal arteriolar diameter in retinal tissue that had been transplanted into hamster cheek pouch membrane. They showed that brimonidine concentrations of up to 10^{-5} M had no effect on vessel caliber. However, until very recently, no clinical studies had been published to determine whether topical brimonidine had any effect on ocular blood flow.

Lachkar and associates[25] performed a double-masked randomized placebo-controlled crossover study that examined the effect of brimonidine tartrate 0.2% on retrobulbar blood flow in patients with ocular hypertension. Using color Doppler ultrasound, they found no significant effect of brimonidine on the blood velocities in the central retinal, ophthalmic, nasal, and temporal ciliary arteries.

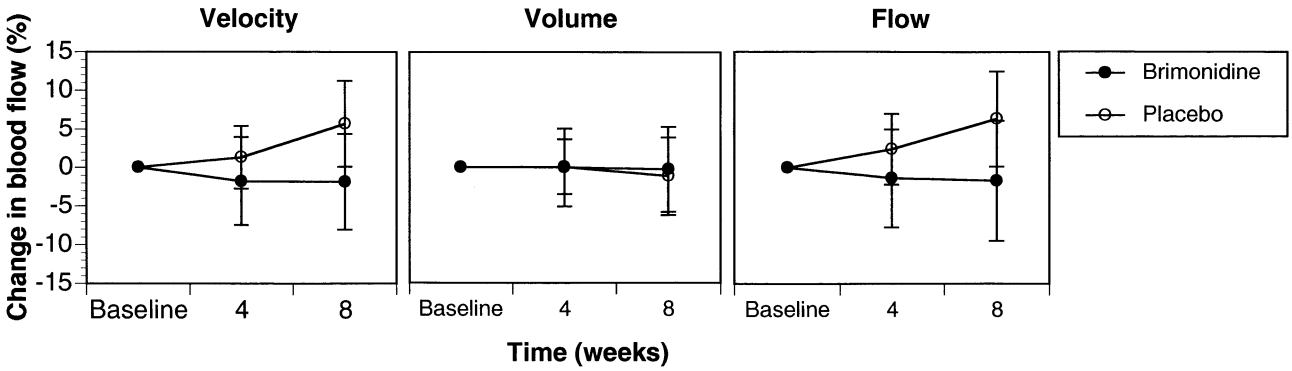

FIGURE 3. Change in the hemodynamic parameters, velocity, volume, and flow at the 4-week and 8-week points from baseline in the brimonidine and placebo groups (error bar = ±1 SE).

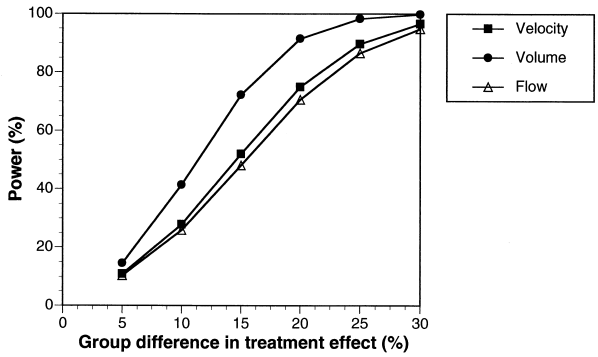

FIGURE 4. Power of the present study (based on a total sample size of 30 patients) to detect differences between the brimonidine and placebo groups of 5% to 30% in treatment effect for the three hemodynamic parameters velocity, volume, and flow. Calculations are based on a type I error (α) of 0.05 and indicate that power greater than or equal to 75% to detect group differences of greater than or equal to 15% for the volume parameter and greater than or equal to 20% for the velocity and flow parameters.

Despite the same general conclusions, their study differed with ours in that they measured blood velocity in the large vessels that supply the whole eye; in our study measurements were taken exclusively from retinal capillary beds. Studies have shown that α_2-adrenoreceptors are distributed differently across arteriolar, precapillary sphincter, and venular segments of various tissue microvascular beds.[18,20] The fact that our results are similar to those of Lachkar and associates suggests that brimonidine has no apparent effect on either large-caliber or small-caliber vessels supplying the retina.

Our study showed that brimonidine significantly reduced intraocular pressure in patients with ocular hypertension. The magnitude of pressure reduction was similar to that reported by Lachkar and associates,[25] whose subjects all had ocular hypertension; however, it was lower than that reported by studies that included patients with glaucoma and patients with ocular hypertension.[2,3,26] It is possible that the composition of the study population may yield different magnitudes of pressure reduction with brimonidine.

Because no difference in the treatment effect in retinal blood flow measurements between the brimonidine and placebo groups was found, we wanted to ensure that our study was adequately powered to determine a clinically significant difference had it existed. Given the variability characteristics of the hemodynamic measurements, we found that we would have detected a group difference in treatment effect of 15% to 20% 75 of 100 times had it existed and a difference of 17% to 23% 80 of 100 times had it existed (Figure 4). Scanning laser Doppler flowmetry has been used successfully to measure a statistically significant increase in retinal blood flow after subjects inhaled carbogen[27] and reduction after they inhaled 100% oxygen.[28] Similar experiments have also been carried out in experimental animals.[29] These data provide a positive control and suggest that confocal scanning laser Doppler flowmetry is capable of measuring changes in blood when they exist.

Using a variety of techniques, investigators have shown that test–retest variability of blood flow measurements, estimated by the coefficient of variation, ranges from approximately 10% to 30%, even within single sessions.[15,16,30–32] Our earlier work suggests that with confocal scanning laser Doppler flowmetry, the largest component of measurement variability is physiologic variation in blood flow from one point in time to another.[17] Given these findings, it is arguable whether detecting differences in treatment effect of less than 15% has much clinical significance, because any beneficial or detrimental drug effects on blood flow should clearly exceed the measured variability. Ideally, any functional consequences of altered blood flow, such as change in the visual field or optic disk, should ultimately be the variables of interest.

The etiology of glaucoma is likely to be multifactorial,

with studies pointing to a possible role for impaired blood flow as one of the potentiating mechanisms of optic nerve damage.[33] In view of the fact that a common initial line of treatment for glaucoma is intraocular pressure reduction with topical adrenergic drugs, it is important to determine whether these drugs have deleterious effects on blood flow. Our study suggests that topical brimonidine reduces intraocular pressure without altering retinal blood flow.

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