Effect of Brimonidine Tartrate on Ocular Hemodynamic Measurements

Yves Lachkar, MD; Clive Migdal, MD; Surinda Dhanjil, MSc, RVT

Objective: To study the effect of a selective α_2-adrenoreceptor agonist, brimonidine tartrate, on ocular hemodynamics.

Subjects and Methods: Eighteen patients with ocular hypertension were enrolled in a prospective, randomized, double-masked study in which 0.2% brimonidine tartrate, administered twice daily, was compared with its vehicle in a crossover fashion. The effect on the ocular circulation was assessed by color Doppler ultrasound, which measured blood flow velocities (peak systolic and end diastolic velocities) in the central retinal, ophthalmic, nasal, and temporal ciliary arteries. The following tests were performed at 2 weekly intervals on both treatments, 0.2% brimonidine tartrate and the placebo: intraocular pressure, heart rate, blood pressure, and color Doppler ultrasound.

Results: Velocities and resistivity indices measured by color Doppler ultrasound in the ophthalmic artery, central retinal artery, nasal artery, and temporal ciliary arteries showed no statistically significant differences between the placebo and 0.2% brimonidine tartrate when compared with baseline values and between the groups. Intraocular pressure was decreased by 17.7% ± 9.5% with 0.2% brimonidine tartrate (vs 9% ± 8% with placebo).

Conclusion: The hemodynamics of the posterior segment of the eye as measured by color Doppler ultrasound do not appear to be altered by 2% brimonidine tartrate.

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W HILE INTRAOCULAR pressure is still considered the main risk factor in the pathophysiology of optic nerve head damage in glaucoma, ischemia of the optic nerve at the level of the lamina cribrosa is also relevant.[1] Current therapy for primary open-angle glaucoma consists of lowering intraocular pressure to a level sufficient to prevent further functional loss.

Brimonidine tartrate (Alphagan, Allergan Inc, Irvine, Calif), a selective α_2-adrenoreceptor agonist, has been shown to decrease intraocular pressure both in the prevention of intraocular pressure elevation following argon laser trabeculoplasty,[2,3] and in the long-term control of intraocular pressure in patients with glaucoma and ocular hypertension.[4] Another α_2-adrenoreceptor agonist, apraclonidine hydrochloride, is known to cause vasoconstriction in anterior segment tissues including the conjunctiva, ciliary body, and iris.[5,6] This vasoconstrictive effect was considered beneficial in decreasing the incidence of postoperative bleeding after laser peripheral iridotomies.[7] It is important, however, to exclude any adverse vascular effect of these compounds, particularly at the optic nerve head.

This study was designed to evaluate whether short-term topical administration of the α_2-adrenoreceptor agonist 0.2% brimonidine tartrate produces any measurable vascular changes at the posterior pole of the eye.

RESULTS

INTRAOCULAR PRESSURE

Mean intraocular pressure ± standard deviation was 24.89 ± 2.76 mm Hg at baseline, 22.67 ± 3.46 mm Hg in the placebo group, and 20.47 ± 3.06 mm Hg in the 0.2% brimonidine tartrate group. Intraocular pressure was significantly decreased by 17.7% ± 9.5% with 0.2% brimonidine tartrate (*P* = .003), vs 9% ± 8% with placebo (*P* = .1). This ocular hypotensive effect in the sequence 2 group (18.2%) was similar in percentage to the sequence 1 group (17.2%). There was no

From the Glaucoma Department, The Western Eye Hospital (Drs Lachkar and Migdal), and the Vascular Surgery Department, St Mary's Hospital (Mr Dhanjil), London, England.

SUBJECTS AND METHODS

In this randomized crossover study, we investigated the effect of 0.2% brimonidine tartrate on the ocular hemodynamics by color Doppler ultrasound (HTI 3000, Advanced Technology Laboratory, Seattle, Wash), measuring blood flow velocity (peak systolic and end diastolic velocities) in the central retinal artery, ophthalmic artery, and nasal and temporal ciliary arteries.

Eighteen patients with ocular hypertension were enrolled in a prospective, randomized, double-masked cross-over study. Following ethical committee approval, informed consent was obtained from all participants. Ocular hypertension was defined as the presence of raised intraocular pressure (>21 mm Hg) without demonstrable visual field defects (program 24-2, Humphrey Visual Field Analyzer 640, Humphrey Instruments, San Leandro, Calif). Exclusion criteria included systemic hypertension, high myopia, diabetes mellitus, vasculopathy (including peripheral vascular disease such as Raynaud syndrome, migraine, and giant cell arteritis), and patients taking oral vasoactive medications including systemic β-blockers or calcium channel blockers. Patients receiving medications that altered blood viscosity or coagulation were also excluded, as were those with a history of previous laser treatment or eye surgery. The mean age of the patients was 55 years (range, 38-66 years). The mean refraction was +0.15 diopters (range, −3 to +3.25 diopters).

Patients were randomized to receive either 0.2% brimonidine tartrate (twice daily) initially for 2 weeks followed by the placebo treatment or vice versa. Ten patients received the placebo followed by brimonidine tartrate (sequence 1) and 8 patients were treated with the reverse sequence (sequence 2). The following tests were performed on 1 eye selected randomly at baseline and at 2 weekly intervals while using each treatment: intraocular pressure (Goldmann applanation tonometry), baseline heart rate (brachial pulse), blood pressure, and color Doppler measurements. All measurements were obtained between 2 and 4 PM.

Tests were performed at 2 weekly intervals because the plasma elimination half-life of brimonidine tartrate is approximately 2 to 5 hours.

Color Doppler measurements were carried out using a color Doppler ultrasound machine (model ADT 3000, Advanced Data Technology, Seattle, Wash). A linear array high-resolution 10-MHz probe was used for imaging of the globe. All measurements were performed by 1 experienced sonographer (S.D.) who was unaware of the subject's clinical status. All examinations were carried out with the patients in a supine position and maintaining fixation. Using the color flow as a map, the central retinal artery was first identified, followed by the ophthalmic artery, and temporal and nasal ciliary arteries. Peak systolic velocities and end diastolic velocities were calculated from the Doppler shifts. At the baseline visit the angle of calculation and the exact site of measurement in a vessel were noted for each vessel of each patient to improve the reproducibility of measurements. On subsequent evaluation, the same angle in each patient was used to calculate the velocities, thus minimizing error. The resistive index was calculated by the method of Pourcelot: resistive indices = (peak systolic velocity – end diastolic velocities)/peak systolic velocity.[8]

Because of the double-masked crossover design of the study, we first analyzed the sequence effect bias by measuring the differences between results calculated for sequence 1 and sequence 2. A t test for period effect was then calculated.[9] A paired t test for normally distributed data, the Student t test, was used to compare the intraocular pressures in the 2 groups. As the distribution of the results was not gaussian, a nonparametric test (the Wilcoxon rank sum test) was used to compare velocity indices and resistive indices. $P<.05$ was considered statistically significant. Bonferroni correction for multiple comparison was used. A sample size of 18 was chosen to provide 90% power to detect a 10% change in flow velocity or resistance in the ophthalmic artery.[10] The sample size provides 90% power to detect a 15% change in the central retinal artery and a 20% change in the posterior ciliary arteries.

significant evidence of a period effect between the 2 sequences ($t = 3.25$; $P>.01$).

CARDIOVASCULAR FACTORS

Mean systolic blood pressure ± standard deviation was 135 ± 15.04 mm Hg at baseline, 137 ± 16.1 mm Hg with placebo ($P = .38$), and 135.3 ± 15.94 mm Hg with 0.2% brimonidine tartrate ($P = .87$ vs baseline and $P = .48$ vs placebo). Mean diastolic blood pressure ± SD was 79.44 ± 14.64 mm Hg at baseline, 83.9 ± 9.3 mm Hg with placebo ($P = .19$), and 83.06 ± 12.38 mm Hg with 0.2% brimonidine tartrate ($P = .23$ vs baseline and $P = .61$ vs placebo). Pulse rate ± SD was 85.44/min ± 7.05/min at baseline, 86.44/min ± 7.56/min with placebo ($P = .58$), and 83.33/min ± 5.48/min with 0.2% brimonidine tartrate ($P = .15$ vs baseline and $P = .43$ vs placebo). There was no significant difference between the 0.2% brimonidine tartrate and the placebo groups for the cardiovascular factors.

COLOR DOPPLER IMAGING

The **Table** shows the mean peak systolic and end diastolic velocities and the mean resistive indices in the central retinal artery, ophthalmic artery, nasal, and temporal ciliary arteries, calculated for baseline, placebo, and 0.2% brimonidine tartrate. There was no significant modification ($P>.05$) between the baseline values and those following drug administration in the central retinal, ophthalmic, nasal, and temporal ciliary arteries for the mean peak systolic and end diastolic velocities and the mean resistive index.

COMMENT

This study found that 0.2% brimonidine tartrate lowered intraocular pressure without significantly modifying measurements of the blood circulation at the posterior segment of the eye. This could be explained by the

Peak Systolic and End Diastolic Velocities and Resistive Indices for All Vessels Studied*

	Baseline	Placebo	P, Baseline/Placebo	Brimonidine	P, Baseline/Placebo
Ophthalmic Artery					
PSV	37.4 ± 9.15	37.57 ± 12.63	. . ./.94	36.11 ± 7.30	.54/.52
EDV	7.82 ± 2.41	7.70 ± 3.00	. . ./.83	8.47 ± 2.14	.16/.38
RI	0.78 ± 0.05	0.78 ± 0.08	. . ./.54	0.76 ± 0.06	.04/.25
Central Retinal Artery					
PSV	10.2 ± 2.64	8.82 ± 3.20	. . ./.08	9.24 ± 3.13	.19/.21
EDV	2.53 ± 0.89	2.32 ± 1.45	. . ./.52	2.55 ± 1.22	.93/.30
RI	0.75 ± 0.08	0.74 ± 0.11	. . ./.42	0.73 ± 0.09	.23/.49
Nasal Ciliary Artery					
PSV	8.70 ± 2.70	7.68 ± 1.77	. . ./.15	8.40 ± 2.60	.72/.36
EDV	2.13 ± 1.01	2.23 ± 0.39	. . ./.50	2.54 ± 0.95	.08/.18
RI	0.76 ± 0.09	0.72 ± 0.11	. . ./.08	0.69 ± 0.10	.02/.36
Temporal Ciliary Artery					
PSV	9.30 ± 4.00	8.37 ± 2.40	. . ./.48	9.18 ± 3.12	.75/.43
EDV	2.55 ± 1.43	2.49 ± 1.23	. . ./.75	2.68 ± 1.30	.77/.26
RI	0.72 ± 0.00	0.71 ± 0.12	. . ./.60	0.71 ± 0.11	.55/.95

*PSV indicates peak systolic velocity; EDV, end diastolic velocity; RI, resistive indices. P values not applicable.

high specificity of brimonidine tartrate for α_2-adrenergic receptors.[11,12]

Many different methods have been used to measure the dynamics of ocular circulation in vivo.[13-20] For technical reasons, wide variations between individuals can occur due to problems related to patient cooperation and posture, as well as a technician's expertise. Furthermore, in glaucoma, it is the blood supply to the retrolaminar portion of the optic nerve head that is relevant, ie, small vessels that are difficult to visualize and have wide anatomic variability.

With color Doppler imaging, good reproducibility of measurements of blood velocities for the ophthalmic artery and the central retinal artery can be obtained (ranges of variability, 6.5%-12.2%).[21] However, the reproducibility of velocities from the posterior ciliary vessels, which are difficult to scan, is poorer than the other vessels (19%-38.8%).[11] In this study, to improve accuracy, we used a 10-MHz probe and documented the image on video to ensure the measurement of the flow at the same location and at the same angle on each successive scanning. This fact is of practical importance, as the angle of the ultrasound beam and the location of the measurements influence the calculations when imaging each artery. A significant velocity gradient exists in the central retinal artery, with the maximum velocity achieved approximately 2 mm from the optic disc in normal subjects.[22] Moreover, as the angle of measurement shifts perpendicular to the direction of flow, the velocity measurement is increasingly underestimated.

The presence of vasoactive α_2 receptors on the orbital vessels is doubtful.[23,24] Yu et al[24] studied the response of isolated human ciliary artery to 9 agonists, concluding that functional histamine, α_1-adrenergic, and serotonin receptors were present on these arteries, but that no α_2-adrenergic receptors were present. A previ-

ous animal study was also unable to demonstrate observable optic nerve vasomotor effects with the α_2-adrenoreceptor agonist apraclonidine hydrochloride.[25]

Brimonidine tartrate was also applied topically to retinal tissue transplanted into the hamster cheek pouch membrane.[26] In this model, the arteriolar calibre in the retinal xenografts was measured by intravital microscopy. Brimonidine tartrate did not cause significant arteriolar vasoconstriction of the human arteriole tissue over a dose range of 10^{-9} to 10^{-4} MAJ evaluated 5 minutes after topical suffusion. Moreover, pharmacokinetic studies in rabbits and monkeys showed that vitreous humor concentrations following administration of 0.2% brimonidine tartrate twice daily for 2 weeks was 10^{-7} MAJ.[2,27,28]

Another animal study investigated the effect of brimonidine tartrate on the optic nerve blood flow in rabbits eyes.[29] Either 0.2% brimonidine tartrate or placebo was applied once daily for 4 weeks. Ocular blood flow was assessed by colored microspheres and vascular corrosion casting. As measured with colored microspheres, optic nerve blood flow was 0.17 ± 0.04 µg/mg per minute in brimonidine tartrate–treated eyes and 0.18 ± 0.06 µg/mg per minute in the placebo-treated eyes. Corrosion casting showed that the average constriction was 16.7% ± 3.7% in brimonidine tartrate–treated eyes, and 16.1% ± 5.3% in the placebo-treated eyes.

Vasoconstriction is mediated mainly via α_1-adrenergic receptors, although α_2-adrenergic receptors may play a part[30] and thereby have a role in the autoregulation of capillary pressure and tissue oxygen delivery. On the other hand, brimonidine tartrate may also produce vasodilatation via the α_2-adrenergic receptors on endothelial cells, which release endothelial-derived relaxing factor.[31,32]

Our results confirmed the beneficial effect of 0.2% brimonidine tartrate on the intraocular pressure. No effect was demonstrated on the pulse rate or systolic and diastolic blood pressure after 15 days of treatment. A previous study in healthy volunteers on the cardiovascular, pulmonary, and ocular hypotensive effects of 0.2% brimonidine tartrate showed a slight reduction in systolic blood pressure during recovery from exercise 4 hours after instillation.[33] In the same study, the ocular hypotensive effect of brimonidine tartrate was comparable with that of timolol and greater than that of betaxolol suspension.

In summary, the lack of effect of brimonidine tartrate on the dynamics of the ocular circulation could be explained by any one or a combination of the following factors: the concentration of the drug at the posterior pole at a level insufficient to affect vasoconstrictive receptors, the release of endothelial-derived relaxing factor, and the absence of α_2-adrenergic receptors on the posterior ciliary arteries.

CONCLUSION

Topically applied 0.2% brimonidine tartrate reduces intraocular pressure, but does not appear to alter the hemodynamics of the posterior segment of the eye as measured by color Doppler ultrasound.

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100 Years Ago in the ARCHIVES

A look at the past . . .

Puccioni describes a cases of bilateral luxation of the lens in a young peasant girl. The lens was dislocated upward and inward in one eye and upward and outward in the other. Since she was much disturbed by asthenopia both lenses were extracted by means of s small flap operation. There having been no trauma and the eyes being otherwise healthy, the author thought the condition to have been brought about by the patient's habit of carrying heavy objects on her head. The straining of the muscles of the neck might so increase the intraocular tension that a weak zonula would be ruptured.

Reference: *Arch Ophthalmol.* 1898;2:320-321.