

Color Doppler imaging study in patients with primary open-angle glaucoma treated with timolol 0.5% and carteolol 2%

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PURPOSE. To evaluate with color Doppler imaging (CDI), in patients with primary open-angle glaucoma (POAG), the possible influence on ocular hemodynamics of a beta-blocking agent with intrinsic sympathomimetic activity (carteolol 2%) compared to a beta-blocker agent without this activity.

METHODS. A study was carried out on 20 patients, with bilateral POAG, intraocular pressure (IOP) ≤ 20 mmHg, all treated twice a day with timolol maleate 0.5% ophthalmic solution. The visual field was evaluated (Octopus 2000 perimeter, G1 program) examining the mean sensitivity (MS) and the mean defect (MD). CDI was carried out to evaluate the resistance index of the internal carotid artery (ICA), the ophthalmic artery (OA), the central retinal artery (CRA), and the short posterior ciliary arteries (SPCA). After these examinations, the therapy was changed to carteolol 2% twice a day. After six months of treatment the examinations were repeated. The data were analysed statistically using Student's *t* test.

RESULTS. The mean intraocular pressure during treatment with timolol 0.5% was 16.7 ± 1.67 mmHg and 16.33 ± 1.72 mmHg after treatment with carteolol 2%, the difference not being significant ($p=0.494$). After six months of treatment with carteolol 2% the MS increased significantly from 22.4 ± 2.5 dB to 24.1 ± 1.8 dB ($p=0.018$), and the mean defect (MD) fell from 5.3 ± 0.8 dB to 4.7 ± 0.6 dB ($p=0.011$). There was no significant difference in the resistance index of the CA, the OA and the CRA with the two treatments, whereas the resistance index of the SPCA dropped significantly, from 0.80 ± 0.05 to 0.77 ± 0.02 ($p = 0.017$).

CONCLUSIONS. CDI did not show significant differences in the resistance indexes of the internal CA, the OA, and the CRA after treatment with carteolol 2% but the resistance index of the SPCA was significantly reduced. Carteolol 2% induced significant changes in the perimetric indexes examined, with an increase in MS and a decrease in MD. These findings suggest that the intrinsic sympathomimetic activity of carteolol may reduce peripheral vascular resistance of the SCA, thus improving perfusion of the optic nerve head, with a protective effect on visual function. (*Eur J Ophthalmol* 2001; 11: 240-4)

KEY WORDS. Color Doppler imaging, Intrinsic sympathomimetic activity, Primary open angle glaucoma

Accepted: January 4, 2001

INTRODUCTION

The etiopathogenesis of primary open angle glaucoma (POAG) has not yet been fully defined. Although elevated intraocular pressure (IOP) is a major risk factor

glaucomatous damage of the optic nerve head may develop at any IOP (1). Other factors, such as vascular ones, may play a role in the genesis of this condition through vasospasm or vasoconstriction with consequent inadequate perfusion of the neural tissue (2-4).

Different methods have been proposed for the study of ocular blood flow in glaucoma: fluorescein angiography (5), the blue field entoptic phenomenon technique (6), ocular blood flow system (7, 8), oculo-oscillo-dynamography (9), laser Doppler flowmetry (10), Doppler ultrasonography (11), and color Doppler imaging (CDI) (12, 13).

The CDI technique uses the Doppler effect and allows the simultaneous visualization of a color-coded vascular map which is overlaid onto a high-resolution conventional B-mode ultrasound image. This non-invasive technique makes it possible to localize and follow the smaller vessels that otherwise would not be identified using a gray scale image. CDI is used not only in the study of glaucoma pathogenesis, but also to evaluate the effect on ocular hemodynamics of some drugs used in the treatment of POAG (13-15).

The present study used CDI to evaluate, in patients with POAG, the possible influence on ocular hemodynamics of a beta-blocker with intrinsic sympathomimetic activity (carteolol 2%) compared to a beta-blocker without this characteristic. Intrinsic sympathomimetic activity may be defined as the residual capacity to stimulate the adrenergic receptors and varies from one beta-blocker to another.

This activity causes a drop in peripheral vascular resistances that may reduce the cardiac side effects (16). In addition it gives better perfusion of the posterior pole of the eye, with the consequent protection of visual function (17).

MATERIALS AND METHODS

From September 1999 to April 2000 we studied 20 patients with bilateral POAG. Eight were male and twelve female and their age ranged from 51 to 59 years (median 56.1). All had been treated with timolol maleate 0.5% ophthalmic solution, twice a day for at least two months, and IOP did not exceed 20 mmHg (mean IOP 16.7 mmHg). All measurements and examinations were carried out by the same two operators. The exclusion criteria were as follows: systemic hypertension, diabetes, ischemic cardiopathy, obstructive pulmonary diseases, obstructive anomalies of the carotid arteries, structural abnormalities of the ophthalmic artery, previous eye surgery, concomitant eye diseases, refractive defects $\geq 2D$.

All the patients underwent the following examinations:

- measurement of systolic and diastolic blood pressure (BP);
- heart rate;
- IOP (tonometric curve) with Goldmann's applanation tonometer;
- evaluation of the visual field using the Octopus 2000 (G1 program) perimeter.

The same operator did these examination, using the same parameters. All the patients had glaucoma at a similar stage, with mean sensitivity (MS) no less than 20dB, and were all experienced with computerized perimetry. MS and the mean defect (MD) were examined;

- CDI was always done by the same operator with an Aloka 2000 machine and a 7.5 Mhz convex probe. The CDI information on blood flow are overlaid in color onto the conventional B-mode ultrasound images. Blood flow is represented with different colors according to the direction of the movement: red is conventionally used to indicate the flow moving towards the exploring probe and blue the flow in the opposite direction. The examination involves positioning the probe on the closed eyelids, coated with methylcellulose, avoiding compressing the eye and keeping the patient in a supine position. Once the vessels are identified, a pulsated Doppler signal is sent. The spectral analysis of this signal appears on the screen and provides information on the blood flow in the vessels examined.

In each patient the following values were determined: the peak systolic velocity (PSV) and the end-diastolic velocity (EDV) of the internal carotid artery (ICA), the ophthalmic artery (OA), the central retinal artery (CRA), and the short posterior temporal ciliary arteries (SPCA).

The data were processed, calculating the Pourcelot's resistance index (RI) that corresponds to the ratio $PSV-EDV/PSV$. The peak systolic and end-diastolic values may be influenced by the operator; in particular the positioning of the probe, if incorrect, changes the direction of the ultrasound wave that strikes the vessels with respect to the direction of the vessel itself (18, 19). The maximum Doppler effect is achieved when the angle between the transmitting probe and the axis of the vessels is zero. Pourcelot's RI not being operator-dependent, is mainly correlated to the dias-

toxic velocity, which is inversely proportional to the peripheral resistances of the circle.

After these examinations, the therapy that was being administered (timolol 0.5%) was changed to carteolol 2%, twice a day. After six months of treatment all examinations were repeated.

For each patient only one eye, was randomly chosen, for a total of 20 eyes.

For statistical analysis the mean values of the parameters examined were compared using Student's t-test.

RESULTS

During treatment with timolol 0.5% mean diastolic BP was 79 ± 7.01 mmHg, mean systolic BP 129 ± 9.2 mmHg and mean heart rate 74 ± 7 beats minute. After six months of treatment with carteolol 2%, mean diastolic BP was 80 ± 6.3 mmHg, mean systolic BP 130 ± 8.1 mmHg and heart rate 77 ± 6.5 pulses per minute. The differences were not significant.

The mean IOP with timolol 0.5% was 16.7 ± 1.67 mmHg, and 16.33 ± 1.72 mmHg, with carteolol 2%, again not significant.

Table I summarizes the mean perimetric indexes examined (MS and MD) after both treatments. Both increased significantly. Table II shows the mean resistance index (RI) of the ICA, OA, CRA and the SPCA arteries after both treatments. There was no significant difference between the RI for the CA, OA and CRA, whereas in the SPCA the RI dropped significantly.

DISCUSSION

At present, the medical treatment of POAG relies mainly on beta-blocking drugs. These lower IOP by inhibiting the production of aqueous humor, probably through a direct action on the epithelium of the ciliary body where the beta-adrenergic receptors (mainly beta-2) are located.

The beta-blockers available for the treatment of glaucoma are numerous and have some common characteristics. However, they differ in several pharmacological properties, such as the intrinsic sympathomimetic activity (ISA), that may be clinically significant.

TABLE I - MEAN SENSITIVITY (MS) AND MEAN DEFECT (MD) AFTER TREATMENT WITH TIMOLOL 0.5% AND CARTEOLOL 2%

	Timolol 0.5%	Carteolol 2%	p
Mean MS (dB)	22.4 ± 2.5	24.1 ± 1.8	0.018
Mean MD (dB)	5.3 ± 0.8	4.7 ± 0.6	0.011

TABLE II - MEAN RESISTANCE INDEXES (RI) IN DIFFERENT VESSELS AFTER TREATMENT WITH TIMOLOL 0.5% AND CARTEOLOL 2%

	Timolol 0.5%	Carteolol 2%	p
ICA	0.74 ± 0.02	0.73 ± 0.03	ns
OA	0.78 ± 0.09	0.76 ± 0.20	ns
CRA	0.81 ± 0.04	0.78 ± 0.10	ns
SPCA	0.80 ± 0.05	0.77 ± 0.02	0.017

ICA = internal carotid artery; OA = ophthalmic artery; CRA = central retinal artery; SPCA = short posterior ciliary artery

Timolol, considered the reference drug among the beta-blockers used in ophthalmology, is a non-selective beta-blocker without ISA. Carteolol is a non-selective beta-blocker that combines a good IOP lowering effect with intrinsic sympathomimetic activity. The results of our study confirm that both drugs have a good IOP lowering effect that persists over time, with no significant differences. Furthermore, carteolol did not have any real effects on the systemic parameters examined.

CDI provides reproducible information about flow velocities in the ICA, the OA, the CRA and the SPCA (1, 10, 20-23). It is important to underline that this technique measures blood velocities and not absolute blood flow, as the vessel diameter cannot be measured with precision *in vivo*. Aside from this limitation, experimental studies have shown a good correlation between blood velocity and blood flow in the brain vessels (24, 25).

CDI has shown that patients with PDAG and normal-pressure glaucoma have lower velocities and higher RI in the retrobulbar vessels than healthy volunteers. This suggests there may be some obstacle to retrobulbar blood flow in glaucomatous patients (26-28).

There are some reports (29) of a significant reduction in the RI of the SPCA in healthy volunteers giv-

en carteolol 2%, suggesting an increase in optic nerve head blood perfusion. Others (14, 30), however, found no significant change in the RI of the CRA and SPCA after timolol 0.5% both in PDAG and in normal-tension glaucoma.

The optic nerve head blood supply is provided mainly by the SPCA and, to a much lesser degree, by the CRA (31). The present CDI investigation found no significant difference in the RI of the ICA, the OA and the CRA after treatment with carteolol 2%, while the RI of the SPCA was significantly reduced. As regards the visual field, significant changes in perimetric indexes were observed after treatment with carteolol 2%, with an increase of the MS and a decrease in MD. These modifications do not seem to be due to a learning effect, since it has been shown that improvements ascribed to this effect take place during the first and second examination, but not usually in later ones (32, 33).

The reproducibility of the CDI results for individual

vessels has been evaluated specifically and some studies (23, 34) report good repeatability of data pertaining to the OA and the CRA; results relating to the SPCA are certainly important and indicative, but they tend to vary more widely, probably because these vessels are so tiny and tortuous. Nevertheless, considering the data we found, it seems that carteolol, with its intrinsic sympathomimetic activity, influences the peripheral vascular resistances of the CPCA, thus improving blood perfusion of the optic nerve head, with a protective effect on visual function.

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