
THE EFFECT OF TOPICAL BETA-ADRENOCEPTOR BLOCKING AGENTS ON PULSATILE OCULAR BLOOD FLOW

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SUMMARY

Thirty-three ocular hypertensive patients (21 with primary open angle glaucoma and 12 glaucoma suspects) were randomly assigned to receive either timolol, levobunolol or betaxolol in one eye. Pulsatile ocular blood flow (POBF) was measured before treatment (baseline) and 2 hours after drop administration. After 1 week of regular twice-daily dosage, POBF was measured again both immediately before and 2 hours after drop instillation. All measurements were made by an investigator masked to treatment. POBF increased by 11% ($p = 0.09$) at week 0 after levobunolol administration, and by 22% ($p = 0.20$) at week 1 before drop administration compared with baseline. It dropped by 23% and 25% ($p = 0.04$ and 0.06 , respectively) before and after betaxolol administration at week 1. Although POBF was reduced in the timolol group, this change was not significant. These results can not be explained uniformly by changes in intraocular pressure or blood pressure. The relevance of these measurements to visual function in glaucoma is not known.

It is generally accepted that reducing intraocular pressure (IOP) can delay or prevent visual field loss in many patients with glaucoma.¹ The most widely used ocular hypotensive drugs are topical beta-adrenoceptor blockers, which lower IOP by reducing aqueous flow. These either act predominantly on beta-1 receptors, or are non-selective and act on both beta-1 and beta-2 receptors. The non-selective drugs are more effective ocular hypotensive agents than are beta-1 selective drugs.²

It is becoming increasingly apparent that risk factors besides high IOP are associated with glaucoma.³ The relationships of some of these risk

factors (e.g. hypertension, diabetes, peripheral vascular disease and vasospasm) to the vascular system suggest that blood flow in the optic nerve head and retina may be altered in glaucoma.⁴ Of the various vascular beds within the posterior segment, the choroidal circulation is of particular interest since it provides the major contribution to the blood flow of the optic nerve at the level of the lamina cribrosa.⁵

Beta-2 adrenergic receptors have been demonstrated in human optic nerve,⁶ as well as in choroidal and retinal blood vessels.⁷ Blockade of these receptors can cause vasoconstriction⁸ which could adversely affect visual function if adequate concentrations of the drug diffused into the posterior segment of the eye or were absorbed systemically. Although it is not possible to measure perfusion of the optic nerve directly or non-invasively, it has been suggested that pulsatile ocular blood flow (POBF) gives an indication by estimating choroidal flow.⁹⁻¹¹

In this study, changes in POBF following instillation of two non-selective agents (timolol and levobunolol) and a beta-1 selective agent (betaxolol) were compared.

SUBJECTS AND METHODS

Thirty-three ocular hypertensive patients (21 with primary open angle glaucoma and 12 glaucoma suspects) were enrolled after their informed consent had been obtained. The mean age of the subjects was 64 years; there were 16 men and 17 women. All patients had at least two occasions. Glaucoma patients had characteristic visual field defects on the Octopus perimeter using programme G1 or 32, and glaucomatous disc cupping. Suspects had normal optic discs and visual fields. Patients were excluded if they had more than 5 dioptres of myopia, were diabetic or were using systemic vasoactive medications. All glaucoma treatment was discontinued for 2 weeks prior to the baseline measurement.

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At the first visit after the washout period (week 0), applanation tonometry was performed and the patient lay supine for 2 minutes. Brachial blood pressure and pulse rate were determined. The eyes were anaesthetised with topical proparacaine hydrochloride 0.5% (Ophthetic, Allergan) and POBF measured with the Langham system (Ocular Blood Flow Laboratories, Annapolis, MD) according to the technique described by Langham *et al.*^{9,10} Four ocular pulse measurements of 5 seconds each were analysed for each eye. To reduce inter-observer bias, all measurements were recorded by the same operator, who was masked to both the treatment and the eye treated. The instrument was calibrated at the start of each session and verified against a silastic membrane at pressures of 15 and 40 mmHg before each patient was tested.

The patients were randomly allocated to receive either 0.5% timolol maleate (Timoptic, MSD), 0.5% levobunolol hydrochloride (Betagan, Allergan) or 0.5% betaxolol hydrochloride (Betoptic, Alcon Laboratories). One drop of the drug was instilled by one of the investigators into the lower fornix of one eye selected at random and the nasolacrimal duct occluded for 2 minutes. All measurements were repeated 2 hours later. The patient was then asked to use the same drop in the same eye twice daily with nasolacrimal duct occlusion for 1 week. At that time (week 1) measurements were repeated again, before and 2 hours after the first drop administration of the day. To minimise the effect of diurnal variation, all measurements were taken between 0800 and 1000 hours.

To assess the reproducibility of POBF measurements, we had previously calculated the coefficient of variation (standard deviation/mean) of three repeated measurements on another 15 glaucoma subjects.¹² The average coefficient of variation was 7.5% and this did not correlate with the magnitude of POBF.

Change in IOP, mean blood pressure and POBF were each compared with baseline (week 0 before drop instillation) using a paired *t*-test for normally distributed data or otherwise its non-parametric equivalent, the Wilcoxon signed rank test. Comparisons were done between treatment groups using the two-sample *t*-test or the Wilcoxon rank sum test, as appropriate. A *p* value of <0.05 was considered significant.

RESULTS

There were no significant differences among patients allocated to each group in terms of age, gender or diagnosis.

Intraocular Pressure

All three drugs reduced IOP in the treated eye over

Table I. Intraocular pressure (mmHg) in the treated eye at each visit before and after instillation of medicine

	Week 0		Week 1	
	Before ^a	After	Before	After
Timolol	25	18 (0.01)	19 (0.01)	19 (0.03)
Levobunolol	27	18 (0.02)	17 (0.01)	17 (0.01)
Betaxolol	25	18 (0.01)	20 (0.02)	17 (0.01)

Figures in parentheses are *p* values for the change from baseline.
^aThe baseline value.

Table II. Mean blood pressure (mmHg) at each visit before and after instillation of medication

	Week 0		Week 1	
	Before ^a	After	Before	After
Timolol	97	98	95	96
Levobunolol	97	98	98	96
Betaxolol	98	96	100	97

^aBaseline value.

Table III. Pulsatile ocular blood flow (μ l/min) in the treated eye at each visit before and after instillation of medication

	Week 0		Week 1	
	Before ^a	After	Before	After
Timolol	498	467 (0.84)	453 (0.99)	408 (0.35)
Levobunolol	492	546 (0.09)	601 (0.20)	518 (0.56)
Betaxolol	483	520 (0.42)	375 (0.04)	364 (0.06)

Figures in brackets are *p* values for the change from baseline.
^aThe baseline value.

the study period (Table I). This ocular hypotensive effect was slightly greater in the levobunolol group (37%) compared with the betaxolol (28%) or timolol (24%) groups, though the differences were not statistically significant.

Cardiovascular Parameters

Mean blood pressure [diastolic + (systolic - diastolic)/3] did not change by more than 2 mmHg in any group (Table II), and there was no significant change in heart rate.

Pulsatile Ocular Blood Flow

Throughout the study period, there was a tendency for POBF to be increased in response to levobunolol and reduced in response to betaxolol. Significance ($p < 0.05$) or trends towards significance ($0.05 < p < 0.10$) were seen for levobunolol at week 0 (11% increase; $p = 0.09$) and for betaxolol at week 1 before and after drop instillation (23% and 25% reduction; $p = 0.04$ and 0.06 , respectively) compared with baseline (Table III). The difference in POBF between these two drugs was highly significant ($p < 0.01$) at week 1 both before and after drop instillation. There was no statistically significant effect on POBF in response to timolol.

Correlations

The changes in POBF and IOP were inversely correlated in the treated eye at week 1 before instillation ($r = -0.39$). There were no other significant correlations between observed changes in POBF and other parameters.

DISCUSSION

In this study, levobunolol increased POBF by 11% after a single dose ($p = 0.09$). This confirms our previous results in which levobunolol was found to increase POBF by 13% in 14 primary open angle glaucoma patients.¹² In addition, we observed a decrease in POBF in response to betaxolol following 1 week of treatment. There was no significant response to timolol.

Several techniques for measuring blood flow non-invasively in human eyes have been proposed. The instrument used in our study measures pulsatile ocular flow. The ocular phase (IOP vs time) is recorded with a pneumatonometer. A pressure-volume relationship for the human eye¹⁵ is then used to derive ocular volume changes.^{9,10} Finally, POBF is determined by calculating the change in ocular volume over time.

Practical and theoretical difficulties are encountered in performing and interpreting POBF measurements with the Langham system. The reliability and reproducibility of the techniques are limited and the instrument needs to be calibrated before each examination session to give comparable readings. In equating POBF with choroidal blood flow, several assumptions are made. First, it is assumed that the majority of ocular blood flow is choroidal. In the monkey, the choroid accounts for over 90% of ocular blood flow.¹⁴ Second, it is assumed that ocular blood flow is predominantly pulsatile. Although diastolic blood velocity in the ophthalmic artery is minimal,¹⁵ it is not known how diastolic blood velocity corresponds to non-pulsatile flow. Because the instrument we used measures only pulsatile flow, it is not possible to recognise changes in the non-pulsatile component. Third, it is assumed that the pressure-volume relationship used by the instrument

to calculate ocular volume is valid for all eyes. However, this relationship was developed from data on only three enucleated and six living eyes.^{9,13} Differences in scleral rigidity, eye volume, and axial length could each affect the derived relationship and, hence, the calculation of ocular blood volume and flow. For example, the accuracy of the technique has been questioned in individuals with high myopia, who are known to have low scleral rigidity and a high axial length.¹⁶

In addition to our previous report,¹² several other studies have looked at changes in pulsatile flow over a few hours after instillation of non-selective topical beta adrenoceptor blocking drugs (Table IV). The results of Yamazaki *et al.*¹⁷ support our finding of no effect on POBF with timolol. In contrast, Yoshida *et al.*¹⁸ found a 30% reduction in POBF in a small number of normal individuals 90 minutes after the instillation of timolol. Grajewski *et al.*⁷ measured pulse amplitude with the same instrument before and 2 hours after timolol administration. They found a decrease with oral but not with topical instillation. After a 2 week treatment period, Trew and Smith¹⁹ found no change in POBF with timolol in most of their glaucoma patients. Bucci *et al.*²⁰ measured ocular pulse amplitude with an earlier version of the Langham system, but did not make a correction for amplitude change due to IOP lowering. After 2 weeks of treatment they found that levobunolol increased POBF; timolol and betaxolol caused no change. Most recently, Boles Carenini *et al.*²¹ noted that after 1 month of treatment POBF was decreased with timolol (not significantly) and levobunolol (significantly) but increased with betaxolol (significantly). The differences among these three groups can be accounted for by differences in pre-treatment POBF; after treatment POBF was remarkably similar. The sample size in the levobunolol group was unsatisfactory with only 4 patients being tested.

These previous studies may not be strictly comparable to the present one, as steps to minimise systemic absorption of drug do not appear to have been taken. In our study, all patients were carefully instructed on the technique of nasolacrimal duct occlusion, and on the day of testing this was supervised by one of the investigators. The lack of change in blood pressure and pulse demonstrates the effectiveness of this procedure. It is unlikely that changes we observed in POBF were due to systemic absorption of the drugs; they are more likely to be due to reduced IOP or diffusion of drug into the posterior segment.

Although the drugs tested are similar in many respects, pharmacokinetic differences among them might be responsible for the results we obtained. Although both timolol and levobunolol are non-selective beta-adrenergic blocking agents with

Table IV. Results of previous studies on ocular blood flow response to topical beta-adrenoceptor (percentage change)

	Betaxolol	Levobunolol	Timolol
<i>Single-dose studies</i>			
Bosem <i>et al.</i> ¹²		+13	
Grajewski <i>et al.</i> ⁷			NS
Yamazaki <i>et al.</i> ¹⁷			NS
Yoshida <i>et al.</i> ¹⁸			-32
<i>One week or more of treatment</i>			
Bucci <i>et al.</i> ²⁰	NS	+7	NS
Morsman (this study)	-22	+11	NS
Trew and Smith ¹⁹			NS
Boles Carenini <i>et al.</i> ²¹	+24	-18	NS

NS, no significant change.

comparable ocular hypotensive actions, their rates of uptake and diffusion may not be the same. After topical administration, levobunolol is transformed in the aqueous into a more polar metabolite, dihydrolevobunolol,²² which may diffuse more slowly into the posterior segment than timolol. This would cause less vasoconstriction and preserve POBF.

Another possible explanation for the differences in POBF between two non-selective agents is differing effects on vascular tone. This could alter the proportion of pulsatile and non-pulsatile flow without affecting the total.

We observed higher POBF in subjects treated with non-selective beta-blockers than with a beta-1 selective agent. After 1 week of treatment there was a significant difference in POBF both before and after drop administration between levobunolol and betaxolol. The increase in POBF after administration of levobunolol could be related to the amount of IOP reduction (37%), as perfusion pressure (mean BP-IOP, where BP is blood pressure) is increased in the absence of vasoconstriction. In support of this, we found that POBF and IOP were inversely correlated after 1 week of treatment before drop administration. This factor alone cannot account for the reduction of POBF seen in the betaxolol group, however. As mentioned above, POBF differences between levobunolol and betaxolol might also be due to changes in the proportion of pulsatile and non-pulsatile blood flow.

The relevance of POBF to the preservation of vision in glaucoma is not fully understood. Optic nerve blood flow is presumably dependent upon both pulsatile and non-pulsatile flow. Although it is often assumed that a higher total blood flow is beneficial, if there were large regional variations then any susceptible tissue, including the optic nerve head, might still be at risk. Even though retinal blood flow is a small component of total ocular blood flow, it may be equally or more important than choroidal flow because of the need to maintain the perfusion of the retinal ganglion cells. Treatment for glaucoma which increases choroidal, retinal and optic nerve blood flow may be desirable, particularly if it lowers IOP concomitantly.

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Key words: Beta blockers, Glaucoma, Ocular blood flow.

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