CLINICAL STUDY

The lack of efficacy of topical beta-blockers, timolol and betaxolol on intraocular pressure in Nigerian healthy volunteers

S.O. OLATEJU, A.A. AJAYI

Abstract

Purpose **The beta-adrenoceptor antagonists are commonly used drugs in ophthalmic and medical practice. While beta-blockers may show reduced antihypertensive efficacy in African patients, the effect of beta-blockers on intraocular pressure (IOP) in African healthy volunteers is less well known.**

Methods **This single-masked, placebo-controlled, randomised study was conducted to investigate the response of healthy Nigerian volunteers to a single drop of the beta-adrenoceptor antagonists timolol and betaxolol. Twenty-five volunteers participated in the study; however, only 19 were able to complete the study. The concentrations of the beta-blocker used were 0.0625%, 0.125%, 0.25% and 0.5%. One eye of the volunteers was used while the other eye served as control. The baseline IOP was documented and IOP measured hourly over 6 h. Pupillary size, corneal sensitivity and visual acuity were also assessed. Cardiovascular parameters were also documented hourly (blood pressure, heart rate, pulse rate).**

Results **Only 0.5% concentrations of both beta-adrenoceptor antagonists caused any significant IOP reduction in normal volunteers ($p < 0.05$). The maximal falls were -2.33 ± 2.2 mmHg and -1.23 ± 0.6 mmHg with timolol and betaxolol, respectively. The IOP reduction produced lasted for only 4 h, after which the IOP returned to baseline. There was also an overshoot of the IOP above the baseline values in all the volunteers (+2.0 to +2.3 mmHg). There was no significant change in the cardiovascular parameters. There was no effect on the pupillary size, visual acuity or corneal sensitivity. There was no significant change in IOP and cardiovascular parameters in the placebo group.**

Conclusions **Both beta-adrenoceptor antagonists caused an attenuated IOP reduction in African normal volunteers, compared with values reported in Caucasians. There was a rebound intraocular hypertensive effect demonstrated with both beta-adrenergic antagonists in blacks.**

Key words Africans, Beta-blockers, Intraocular pressure

Beta-adrenoceptor blockers are important drugs in ophthalmic and medical practice. They were first used in the medical management of systemic hypertension, but their hypotensive effect in the management of ocular hypertension and glaucoma was incidental. Philips *et al.*[1] first demonstrated in 1967 the intraocular pressure (IOP) lowering effect in human eyes. Since then, various studies have been carried out to demonstrate the IOP lowering effects, but only a few of the drugs were found suitable when applied topically.[2,3] Beta-adrenoceptor blockers reduce IOP by reducing the aqueous humour production only and do not seem to have any significant effect on the outflow facility of aqueous drainage.[3–6]

Various studies have demonstrated the efficacy and safety of the common topical beta adrenergic antagonists in reducing IOP in healthy volunteers and glaucoma patients. The systemic beta-adrenergic blockers used in essential hypertension have been found not to be as effective in Africans as they are in Caucasians.[7–11] The implication is that there are some racial variations in the blood pressure response to the beta-adrenergic antagonists which may be related to differences in plasma renin activity.

We are unaware of any study to demonstrate and characterise the response of the beta-receptors in the eye of Nigerians healthy volunteers to beta-receptor antagonist therapy. This may help to predict the response of glaucoma patients, since an abnormal beta-receptor response has been demonstrated in glaucoma patients.[12]

S.O. Olateju
Department of Surgery
(Ophthalmology Unit)
Obafemi Awolowo
University
Ile-Ife, Nigeria

A.A. Ajayi
Department of Medicine
Obafemi Awolowo
University
Ile-Ife, Nigeria

Dr S.O. Olateju ✉
Ophthalmology Unit
Department of Surgery
Obafemi Awolowo
University
Teaching Hospitals Complex
PMB 5538, Ile-Ife
Osun State, Nigeria
Fax: +36 230141
e-mail:
molateju@oauife.ed.ng

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Materials and methods

Volunteer selection

A single-masked, placebo-controlled, randomised, parallel group study was undertaken. The study protocol was reviewed and approved by the Obafemi Awolowo University Teaching Hospitals Complex Ethics Committee. The criteria for inclusion in the studies were: (i) IOP within the normal range (≤ 18 mmHg) on two different occasions; (ii) optic nerve head : cup disc ratio ≤ 0.4; (iii) open anterior chamber angle on gonioscopy; (iv) not on any systemic medication for any condition; (v) no known cardiovascular or respiratory problems; (vi) age ≤ 40 years. Subjects were excluded on the basis of: (i) a history or recent ocular inflammation or trauma; (ii) embedded foreign body within 1 month prior to the study; (iii) active hepatic keratitis or corneal ulcer within 3 months prior to the study; (iv) any corneal abnormalities preventing reliable applanation tonometry; (v) asthma or chronic obstructive airways disease; (vi) first degree heart block; (vii) sinus bradycardia; (viii) pregnancy or lactation. Altogether, 25 healthy volunteers were recruited into the study. The participants were randomized into three groups for the two groups (timolol and betaxolol) and placebo.

Examination procedure

Of the 25 healthy volunteers who fulfilled the above criteria, only 19 completed the study. Six were excluded for violating the study protocol by not reporting for measurements when required.

Goldmann applanation tonometry was used to measure the IOP throughout the period of the study. Three IOP measurements were taken; the average of two consistent reading was the IOP recorded. To ensure standardisation of the IOP, the Goldmann tonometer was calibrated with the normal standard. One of the investigators measured the IOP for all the volunteers throughout the study period after a period of test and retest of IOP in a known ocular hypertensive to ensure accurate measurement. The examinations carried out included anterior and posterior segment examination with pen-torch, slit-lamp and bilateral indirect ophthalmoscopy to exclude any pathology. Indirect gonioscopy was also done to access the anterior chamber angle. Measurement of baseline pulse rate, blood pressure and electrocardiography (ECG) were also undertaken.

The following concentrations of betaxolol hydrochloride and timolol maleate were tested sequentially with a washout period of at least 24 h between different concentrations: 0.0625%, 0.125%, 0.25% and 0.5%. A drop of the test beta-blocker was applied into one eye while the second eye served as a control. The following parameters were recorded every hour for 6 h: IOP, pupil size, blood pressure (BP), pulse rate (PR), heart rate (HR) and corneal sensitivity. The same procedure was repeated for both betaxolol and timolol in the subjects. Corneal sensitivity was tested and graded as either intact, decreased or absent. Visual acuity and pupillary size were also assessed. The change in IOP recorded in this study represents the difference between the baseline IOP and IOP per hour in the treated eye, as in some earlier studies.[2,11] The second eye was used to study the systemic effect of the drugs.

Statistical analysis

Data are expressed as the mean ± SD. To determine whether there is any statistical difference in the effect of the two beta-blockers in their IOP lowering effect, repeated measures analysis of variance (ANOVA) and the *F*-test were used. The ANOVA included a treatment effect, and time × treatment interaction analysis. Correlations between the different drug concentrations and various clinical effects were determined by linear regression analysis. Statistical significance was accepted at $p < 0.05$.

Results

The study population characteristics are summarised in Table 1. There was no significant effect on the cardiovascular parameters – blood pressure, pulse rate and heart rate – from any of the concentrations of timolol used. Baseline HR, PR and BP were 67.33 ± 4.42/min, 70.17 ± 4.66/min and 91.67 ± 3.65/65 ± 3.16 mmHg; equivalent values at 6 h were 66.67 ± 3.89/min, 72.67 ± 2.90/min and 93.33 ± 4.78/66.67 ± 4.67 mmHg.

Table 2 summarises the change in IOP per hour per concentration of the test drugs and hourly change in IOP for placebo.

The IOP values among the patients were fairly symmetrical. Topical beta-blockers – betaxolol hydrochloride (0.25% and 0.5%) and timolol maleate (0.25% and 0.5%) – were found to have slight ocular hypotensive effects in the healthy normal volunteers. The peak hypotensive effect was produced at 2 h and lasted for a maximum of 4 h. There was no hypotensive effect seen in the placebo group. Drug concentrations below 0.25% for either drug were not effective in producing an IOP reduction. Both drugs were safe when applied to normal volunteers and produced no significant effect on the cardiovascular parameters. The cardiovascular effects were more pronounced in the timolol group than the betaxolol group, while the placebo group did not show any cardiovascular effect.

Timolol maleate

Timolol maleate (0.5%) produced a maximum change of −2.33 ± 2.27 mmHg from the pre-treatment IOP after the first hour and this was sustained for 2 h, after which the pretreatment IOP was attained by the fourth hour ($p < 0.05$, ANOVA compared with placebo and baseline). There appeared to be an overshoot in the IOP between 5 and 6 h and a rebound phenomenon was also observed. The maximum overshoot was +2.0 ± 3.2 mmHg.

Table 1. *Basic parameters for the healthy volunteers*

	Placebo (n = 5)	Betaxolol (n = 8)	Timolol (n = 6)
Age (years)	25.80 ± 2.53	27.63 ± 4.38	26.83 ± 3.50
Sex (M:F)	2:3	3:5	2:4
IOP (mmHg) at 0 h			
Right	13.20 ± 1.47	13.75 ± 1.2	13.80 ± 1.87
Left	13.20 ± 1.47	13.75 ± 1.2	13.80 ± 1.87
IOP (mmHg) at 6 h			
Right	13.20 ± 1.47	14.63 ± 0.35	15.83 ± 2.06
Left	13.20 ± 1.47	15.25 ± 1.20	14.83 ± 1.89
SBP (mmHg) at 0 h	100 ± 6.32	96.25 ± 12.18	91.67 ± 3.65
DBP (mmHg) at 0 h	70 ± 00	63.75 ± 6.96	65 ± 3.16
SBP (mmHg) at 6 h	98 ± 40	97.5 ± 9.68	93.33 ± 4.78
DBP (mmHg) at 6 h	70 ± 0	63.75 ± 6.96	66.67 ± 4.67
HR (beats/min) at 0 h	70.8 ± 2.03	72.5 ± 4.09	67.33 ± 4.24
HR (beats/min) at 6 h	70.8 ± 2.04	69.75 ± 5.05	66.67 ± 3.89
PR (min^{-1}) at 0 h	69.40 ± 2.33	71.25 ± 5.57	70.17 ± 4.66
PR (min^{-1}) at 6 h	69.40 ± 2.32	70.88 ± 5.97	72.67 ± 2.90

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; PR, pulse rate.

The curve of timolol concentration versus IOP was sigmoid (Fig. 1) and there was a shift to the right. The maximal IOP fall of −2.33 ± 2.27 mmHg was produced by 0.50% timolol, while 0.25% timolol caused a maximum fall of −1.25 ± 1.61 mmHg of 2 h duration. Concentrations below 0.25% did not produce any effect on IOP. There was no effect on the visual acuity, pupillary size or corneal sensitivity throughout the test period by any of the drug concentrations used.

Betaxolol hydrochloride

Betaxolol hydrochloride, a $beta_1$-specific antagonist, produced a maximum fall in IOP of −1.25 ± 1.71 mmHg at 2 h. This is less than that produced by timolol maleate (−2.33 ± 2.27 mmHg). The fall in IOP was sustained for 4 h followed by a rebound increase at 5–6 h. The effect of 0.5% timolol peaked rapidly compared with betaxolol, whose action appeared to be more sustained. Betaxolol at 0.25% produced a fall in IOP (−1.0 ± 1.58 mmHg) at 2 h, unlike timolol, which produced no reduction in IOP and enhanced rebound phenomenon. At 0.5% concentration betaxolol produced its maximum IOP reduction at 2 h.

Fig. 1 shows the dose–response curve for the two drugs. Timolol caused a greater fall in IOP compared with betaxolol ($p < 0.05$). The effect of betaxolol appeared to be better sustained than that of timolol. The reduction in IOP produced by 0.25% betaxolol is more than that produced by timolol of the same concentration. Timolol 0.50% caused a significantly lower heart rate compared with betaxolol 0.5% ($p < 0.02$). Betaxolol appears to possess an ocular effect and cardiac sparing effect. This implies that timolol may have a greater ocular effect but less cardiac sparing than betaxolol. There was no effect on visual acuity, pupillary size and corneal sensitivity throughout the test period by any drug concentration used.

Placebo

The placebo used was water for injection applied with the same standard dropper as for the test drugs. There were 5 normal volunteers in the placebo group. This was to exclude the possibility of observer bias for any response likely to be produced by the test drug on the volunteers.

Table 2. *Mean change in intraocular pressure (IOP; mmHg) per hour in treated eyes*

	0.5%		0.25%		0.125%		0.0625%		
Hours	Timolol (n = 6)	Betaxolol (n = 8)	Timolol (n = 6)	Betaxolol (n = 8)	Timolol (n = 6)	Betaxolol (n = 8)	Timolol (n = 6)	Betaxolol (n = 8)	Placebo
1	−2.33 ± 2.27	−1.23 ± 0.60	−0.50 ± 2.12	−0.63 ± 2.38	+0.17 ± 2.77	+0.38 ± 1.58	+1.50 ± 1.53	+0.88 ± 1.22	13.20 ± 1.47
2	−2.17 ± 0.97	−1.25 ± 1.64	−0.17 ± 1.16	−1.0 ± 1.58	0.00 ± 2.71	+0.88 ± 1.22	+1.33 ± 1.73	+0.88 ± 1.22	13.20 ± 1.47
3	−1.33 ± 3.47	−1.25 ± 1.64	+0.33 ± 0.997	+0.13 ± 3.01	+1.67 ± 1.68	+1.13 ± 1.998	+0.67 ± 0.99	+0.88 ± 1.22	13.20 ± 1.47
4	−0.83 ± 1.42	−0.50 ± 1.32	+1.33 ± 1.42	+0.38 ± 2.05	+0.83 ± 1.42	+0.75 ± 1.22	+0.17 ± 0.70	+0.13 ± 1.41	13.20 ± 1.47
5	+1.17 ± 3.67	+0.38 ± 3.74	+0.17 ± 1.41	+0.75 ± 1.64	+1.67 ± 1.73	+0.75 ± 1.00	+0.50 ± 0.50	+0.75 ± 0.71	13.20 ± 1.47
6	+2.00 ± 3.20	+2.33 ± 1.28	+1.17 ± 1.15	+0.75 ± 1.63	+1.17 ± 1.63	+0.75 ± 1.32	+0.33 ± 1.0	+0.88 ± 1.22	13.20 ± 1.47

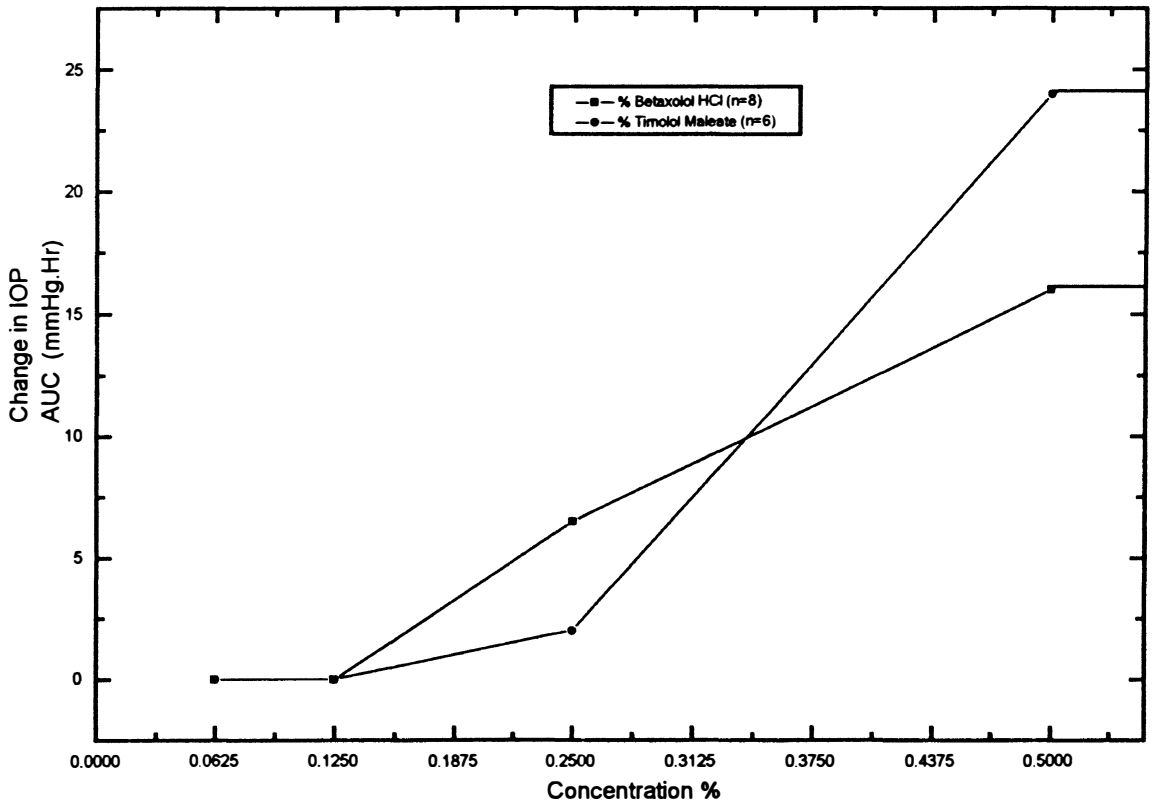

Fig. 1. *Dose–response curves of betaxolol hydrochloride and timolol maleate.*

There was no IOP reduction or overshoot above the baseline throughout the 6 h test period. There was no significant alteration in the cardiovascular parameters in the placebo group. The pre-treatment state was maintained for all the above parameters after 6 h.

Discussion

In the present study, the topical beta-blockers timolol maleate and betaxolol caused a slight ocular hypotensive effect in Nigerian healthy volunteers.

The limitations of these investigations, which included a drop-out among the volunteers, non-availability of the drugs at a concentration of 1% and lack of laser pupillometry, were anticipated. The drop-out might have been due to lack of incentive for a mechanistic study, since each of the subjects was studied four times for a period of 6 h each time. Drug concentrations more than 0.5% are not available commercially.

We used a repeated measures design so that we had an increase in the degrees of freedom, greater power and less chance of a type 2 error. Furthermore, a single drop of test drug was used rather than preloading the volunteers to simulate clinical treatment, whereby a patient is commenced on therapy on confirmation of diagnosis. To our knowledge no pharmacodynamic study in black healthy volunteers has ever been undertaken.

The poor ocular hypotensive effects of topical beta-blockers in normal volunteers suggest that the same subtypes of beta-adrenoceptor control IOP and cardiovascular homeostasis, in which a poor response has been reported in Africans.[7–10]

The IOP fall produced occurred within the first 2 h after treatment. This hypotensive effect did not last for up to 6 h, contrary to the finding in studies in Caucasians that a single drop could produce an effect lasting up to 24 h.[3] The IOP reduction produced by betaxolol was well sustained compared with the effect of timolol, which peaked rapidly but was not sustained. This might have a relative advantage in glaucoma patients, who need to have a well-sustained IOP reduction. An effective drug for IOP control should produce a statistically significant IOP reduction within the first 24 h of application. The effect should also be sustained in the long term. There was no statistically significant difference between men and women in the IOP response to topical beta-blocker irrespective of the concentration of the drug. This probably indicates that there is no hormonal influence in the response of the adrenergic receptors to topical beta-blockers.

There was only a slight treatment effect ($p < 0.05$) on IOP using a 0.5% concentration and a slight dose dependency effect as revealed by a greater IOP reduction produced by 0.5% drug concentration. There was no treatment time × drug interaction observed in this study. Furthermore there was a shift to the right in the

dose–response curve, hence the lesser sensitivity of Nigerians to beta-antagonists. This underscores the need to try a 1% drug concentration among Nigerians. A concentration of 0.125% did not produce any significant ocular hypotensive effect, contrary to an earlier study in Caucasians which suggested that a concentration as low as 0.1% could be effective.[3] The effect demonstrated in Nigerians might be due to the population of beta-receptors (β-max) as well as signal transduction being reduced or less effective in African subjects.[9]

Betaxolol produced a greater cardiac sparing effect than timolol. It also had a similar ocular hypotensive effect to that produced by timolol. In view of this, betaxolol may be safer for the elderly patients who are also prone to cardiovascular problems. There was a statistically significant difference in the fall in heart rate produced by timolol compared with betaxolol. It is known that there is interaction between systemic beta-blocker and topical beta-blockers. The addition of a systemic beta-blocker to a patient already on a topical beta-blocker provides little additional lowering effect of the IOP, probably because the customary topical doses are enough in themselves to elicit a maximal response. In a large meta-analysis it was found that topical anti-glaucoma therapy (beta-blocker inclusive) did not have any significant effect on cardiovascular outcome in patients.[13] In addition, the relative risks of pacemaker placement were not increased among subjects who were current users of glaucoma medications.[13] This underscores the overall cardiac sparing effect and safety of ocular beta-blockers.

There was no reduction in the distant and near vision relative to the pretreatment vision. This is consistent with previous reports that topical beta-blockers do not have any effect on visual acuity. The corneal sensitivity was intact throughout the study period. This finding corroborates the fact that topical timolol has a pure beta-blocking effect but lacks the intrinsic sympathomimetic activity and membrane stabilising effect that is present in some beta-blockers such as alprenolol and oxprenolol.[14]

The pattern of response produced by the normal volunteers to betaxolol and timolol is similar. This is not unexpected as both are beta blockers except that betaxolol hydrochloride is a $beta_1$-selective antagonist. The maximal IOP reduction was produced by a 0.5% concentration of the drugs while no appreciable response was observed with concentrations of −0.125% and 0.0625%. This contrasts with the finding that timolol is effective even at a concentration of 0.1%.[3] Betaxolol 0.25% seems to possess a greater ocular hypotensive effect than timolol 0.25%. Lipophilicity of the drugs might account for this.

The IOP reduction produced in the normal volunteers by a single drop of either of the test drugs lasted between 2 and 4 h. This contrasts with the findings of Katz *et al.*[11] who found an IOP reducing effect of timolol lasting up to 7 h. The findings of another investigator that a single drop of timolol maleate produced an IOP reduction lasting up to 24 h was not confirmed in this study.[2,3] The finding corroborates the earlier observation that there is a racial difference in the response to beta-adrenoceptor antagonists and also that beta-adrenoceptor antagonists are not as effective in Africans as in Caucasians in the treatment of essential hypertension.[9,10]

Another significant observation from the normal volunteers is that there is a 'rebound phenomenon' of IOP rise 4 h after a single drop of the test drug. The implication of this might be that this is the pattern of action in a glaucoma patient on any of the beta-blockers on stopping the drug due to poor compliance for any reason (e.g. non-availability of the drugs, lack of funds or fake drugs) which commonly occur in poor socioeconomic groups in the African setting. The effect might be similar to that produced by some systemic anti-hypertensives, such as clonidine, with rebound effect. Rebound has been described in angina on stopping beta-blocker too. The implication of this observation might be that the IOP between doses might be increasing once the effect of the applied dose is over. Another dose of the drug at the point of inflexion of IOP reduction to the rise in IOP may produce a further reduction in IOP. This probably indicates a necessity for a dose adjustment in African glaucoma patients as against the current practice of a 12 hourly regime for topical beta-adrenoceptor antagonist. Racial differences in the response to beta-blockers might be responsible for this. An intrinsic sympathomimetic effect of timolol at ultralow doses in the eye is a conjectural possibility.

The IOP lowering effect of both test drugs seems to increase with increasing concentration of the drugs. This is in support of studies in which a further reduction in IOP is associated with an increased concentration of the beta-blocker, but there was no significant difference once the concentration of timolol was above 1%.[3]

The cardiovascular effect produced in the normal volunteers based on the heart rate and the pulse rate evaluation is non-significant, and none of the volunteers demonstrated significant bradycardia at any drug concentration used. There was no significant effect produced on the distance and near acuity. Pupillary size and corneal sensation were not affected. All these findings also agree with previous reports that beta blockers do no have any significant effect on the aforementioned parameters.[2]

In conclusion:

1. Topical beta-blocker produced a slight IOP lowering effect in African normal volunteers which is very much less than the reported values in Caucasians at the same doses.
2. There is a rebound effect within the first 6 h of application of the test drug. Dose adjustments or dose interval modification might be necessary for Africans.
3. There was no statistically significant effect on the cardiovascular parameters in the normal volunteers even with the highest available concentration. Pupillary size, distance and near acuity are spared and corneal sensitivity preserved.

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