Ocular and cardiovascular response to topical carteolol 2% and timolol 0.5% in healthy volunteers

D J BRAZIER AND S E SMITH

From the Department of Clinical Pharmacology, St Thomas's Hospital Medical School (UMDS), London SE1 7EH

SUMMARY Ocular and cardiovascular effects of carteolol 2%, timolol 0.5%, and dummy eyedrops have been measured in a single dose double-blind crossover study in six healthy volunteers. Both drugs lowered intraocular pressure and reduced exercise-induced tachycardia. Neither produced a significant change in resting heart rate or blood pressure. The two agents appear comparable as regards ocular hypotensive and cardiovascular effects.

Topical beta adrenoceptor blocking drugs (beta blockers) are now the first line of treatment in many types of glaucoma, though their use in certain individuals is restricted by adverse cardiovascular or respiratory effects resulting from systemic absorption. Timolol has been reported to cause bradycardia, syncope, arrhythmias, and exacerbation of obstructive airways disease.¹ In theory beta blockers with differing properties such as cardioselectivity, partial agonist activity (intrinsic sympathomimetic activity; ISA) or reduced lipid solubility should offer advantages over timolol with respect to these adverse effects. This paper reports a comparative study of intraocular pressure (IOP) and cardiovascular effects of timolol and the newly introduced topical beta blocker, carteolol.

Material and methods

SUBJECTS

Six healthy subjects, three female and three male, aged 33 to 57 years, took part in this study. None had a previous history of cardiovascular or respiratory disease or was taking drugs of any kind. All had normal eyes, IOPs, blood pressure, peak expiratory flow, electrocardiogram, blood count, and electrolytes. The subjects were phenotyped for debrisoquine hydroxylation,² and all were extensive metabolisers (range of metabolic ratios 0.2 to 1.7). Non-metabolisers of debrisoquine were excluded

because they may be prone to prolonged effects from small systemic doses of certain beta blockers.

Each gave written consent to participate and the study was approved by the Ethical Committee of West Lambeth Health Authority.

TREATMENTS AND STUDY DESIGN

Subjects attended on three occasions at the same time of day separated by at least seven days. On each occasion one of three treatments, carteolol 2%, timolol 0.5%, or a matching dummy solution, was administered double blind as eyedrops in a complete balanced crossover design. Two drops of drug solution (volume 0.027 ml each) were applied one minute apart to one eye, the same eye being used in each volunteer for all treatments.

MEASUREMENTS

Before and 2 and 4 hours after treatments the following measurements were made in the order given. The IOP was measured by applanation tonometry under proxymetacaine 0.5% local anaesthesia. Three readings were recorded from each eye on each occasion, the tonometer dial being read by an independent observer. Following a 10-minute supine rest period, the heart rate (HR) was recorded from an electrocardiography (ECG) and blood pressure (BP) measured by sphygmomanometry. The BP was recorded as mean BP (diastolic plus one-third pulse pressure). The HR was then measured during the last 15 seconds of an exercise period on a bicycle ergometer. The exercise level and duration had been set by a preliminary study to give an increase of heart

Correspondence to Mr D J Brazier, FRCS, Department of Clinical Pharmacology, St Thomas's Hospital Medical School (UMDS), Lambeth Palace Road, London SE1 7EH.

rate of 80–100 beats per minute, a tachycardia of over 140 beats per minute in all subjects.

STATISTICAL ANALYSIS

Repeatability of the baseline measurements was derived from within-subject variation by analysis of variance, by means of standard methods, and expressed as a coefficient of variation (%). The findings were:

Between occasions: IOP	11.6%
resting HR	6.9%
exercise HR	3.7%
resting BP	3.8%
Within occasions: IOP	6.7%

Fig. 1 Intraocular pressure (mmHg) in treated and untreated eyes before and after instillation of carteolol 2% (●—●), timolol 0.5% (Δ—Δ), and dummy (○-----○) eyedrops.

Differences in IOP, resting and exercise HR, and BP were analysed by paired *t* tests.

Results

INTRAOCULAR PRESSURE

IOP values for treated and untreated eyes are shown in Fig. 1. By comparison with the dummy treatment both beta blockers produced significant falls in IOP at 2 hours ($p < 0.05$) and 4 hours ($p < 0.05$) after instillation. In each case maximum responses were reached at 4 hours, the pressure falls being carteolol 2.2 ± 0.6 mmHg and timolol 2.3 ± 0.7 mmHg (mean $\pm$ SEM).

Fig. 2 Exercise heart rate (beats per min), mean blood pressure (mmHg), and resting heart rate (beats per min) before and after instillation of carteolol 2% (●—●), timolol 0.5% (Δ—Δ), and dummy (○-----○) eyedrops.

There was no significant difference between the two drug effects.

The IOP responses of the untreated eyes were largely obscured by differences in starting pressure. Despite this, however, carteolol produced a significant fall at 4 hours (1.2 ± 0.3 mmHg, $p < 0.05$).

CARDIOVASCULAR SYSTEM

The cardiovascular changes observed are shown in Fig. 2. Neither drug had a significant effect on resting HR or BP.

Both carteolol and timolol reduced exercise heart rate. The drug effects were greatest at 2 hours after instillation, amounting to: carteolol 22 ± 4 beats per min ($p < 0.01$), timolol 12 ± 3 beats per min ($p < 0.01$) (mean $\pm$ SEM). At 4 hours the effect of carteolol was somewhat greater than that of timolol ($p < 0.05$). Impaired exercise responses were associated with calf pain in some subjects.

Discussion

A number of beta blocking agents have recently become available for topical use in glaucoma. Their introduction raises two questions: firstly, will the new agents reduce IOP as well as or better than the established drug timolol; and, secondly, can this effect be achieved with equal or reduced systemic cardiovascular or respiratory side effects?

With regard to the first question it appears in this study of healthy volunteers that IOP reduction with carteolol 2% is not significantly different from that with timolol 0.5%. A recent similar study has shown no difference of hypotensive effect of metipranolol, another recently introduced agent, and timolol in glaucoma patients.³ Betaxolol may produce less IOP reduction than timolol in glaucomatous eyes.⁴

The incidence of systemic complications of topical beta blockers is theoretically influenced by pharmacological properties of the different drugs. It has been suggested that the property of ISA, possessed by carteolol, may prevent reduction of resting heart rate which occurs when this property is absent. We did not

identify a significant difference between carteolol and timolol in this respect.

For the strengths of carteolol and timolol drops used in this study it appears that carteolol reduces exercise induced tachycardia to an equal or greater extent than timolol. Our observations suggest that carteolol does not have any significant advantage or disadvantage as a topically applied beta blocker over timolol as far as IOP and cardiovascular effects are concerned.

Betaxolol is a cardioselective beta blocker, which should make it safer than non-selective agents in patients with lung disease. Van Buskirk *et al.*⁵ reported its use in asthmatic patients without deterioration of pulmonary function. However, exacerbation of obstructive airways disease can occur with betaxolol,⁶ indicating that its cardioselectivity is not absolute.

These examples of variation between theoretical and actual effects of topical beta blockers suggest that a period of evaluation is required before their place in treatment can be established.

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