

Ocular responses in healthy subjects to topical bunazosin 0.3% – an α_1 -adrenoceptor antagonist

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Abstract

The ocular effects of the α -adrenoceptor blocking drug bunazosin, administered as eyedrops, have been measured in a placebo-controlled double-blind single-dose study in 15 healthy volunteers. The drug significantly reduced intraocular pressure over 10 hours, and there was no associated change in pulsatile ocular blood flow. Characteristic effects of α -adrenoceptor blockade were observed – miosis, ptosis, and conjunctival hyperaemia. The miosis alone persisted for more than 24 hours in nine out of 15 subjects.

Lowering of intraocular pressure by local sympathetic blockade¹ provides the commonest basis for the medical management of chronic simple glaucoma, in which pressure is usually high. Long term administration of β adrenoceptor antagonists successfully controls intraocular pressure,² yet in many patients visual field loss continues and vision deteriorates.³ One factor which could be involved is a progressive diminution of the blood supply to the posterior segment of the eye. Timolol has been shown to cause vasoconstriction in human retinal arteries⁴ and to have similar effects associated with a decreased blood flow to the optic nerve head and choroid in experimental animals.⁵ We have previously shown that patients suffering from chronic open angle glaucoma have a reduced pulsatile ocular blood flow and that this was not improved by the use of topical timolol.⁶ Agents which improve local circulation may help to prevent visual deterioration.

Bunazosin is a vasodilator, an analogue of the α receptor antagonist prazosin which is widely used in the treatment of systemic hypertension⁷ and which has been found to lower intraocular pressure in animal studies by suppression of aqueous formation rather than a change in outflow.^{8,9} Information of a similar nature is also available for topically applied bunazosin in a few human volunteers.¹⁰ In these studies its topical application has been shown to cause minor irritation only.

The study of α -adrenergic receptors in the eye is receiving increasing interest, particularly in the field of glaucoma research. Recent reviews have highlighted the hypotensive effects of both antagonists¹¹ and agonists such as clonidine (α -2)¹², and these or related agents may well provide the basis for future therapeutic action.

In addition to their hypotensive action, α -adrenergic drugs may have an important effect on blood vessels in the eye, affecting supply to critical areas of the retina, choroid, and disc. Catecholamine binding sites have been demonstrated in the retinal vessels of animals,¹³ though

whether they are present in human eyes is not yet known.

The present study has been undertaken, therefore, to record the effects of topical application of bunazosin 0.3% on intraocular pressure and pulsatile ocular blood flow and to evaluate any disadvantages and risks associated with their use.

Materials and methods

SUBJECTS

Fifteen healthy subjects (seven male, eight female) aged 20-59 years were recruited to the study. All were of normal height and weight and none were found to have any abnormality on ocular, cardiovascular, and general medical examination or in haematological or biochemical profiles. Each gave written consent to participate, and the study was approved by the Ethics Committee of West Lambeth Health Authority.

TREATMENTS AND STUDY DESIGN

Bunazosin 0.3% and a matching 'vehicle only' solution were administered double blind as eyedrops, one to each eye. The eyes were randomly assigned to bunazosin or vehicle eyedrops which were contained in identical and consecutively numbered vials for each subject. Formulation and packaging was performed by Dispersa Ltd, and the code was held by them throughout the trial.

Subjects attended on one occasion, in the morning. Two drops of either drug or vehicle solution were instilled 30 seconds apart to one eye and the same procedure followed for the second eye with the second numbered vial.

MEASUREMENTS

The following measurements were performed before and at various times after eyedrop instillation:

(1) Pupil diameters were measured by infrared TV pupillography, after 30 seconds in darkness, with a Whittaker 1800 series pupillometer, prior to eyedrop instillation and at 1, 2, 6, 10, and 24 hours.

(2) Eyelid positions were recorded with a Yashica Dental-Eye camera with the subject's gaze at infinity. The palpebral height was measured, on projection, through the midpoint of the pupil. Measurements were performed prior to eyedrop instillation and at 1, 2, 6, and 10 hours.

(3) Intraocular pressure was measured by Goldmann applanation tonometry, under benoxinate 0.4% local anaesthesia, in the sitting

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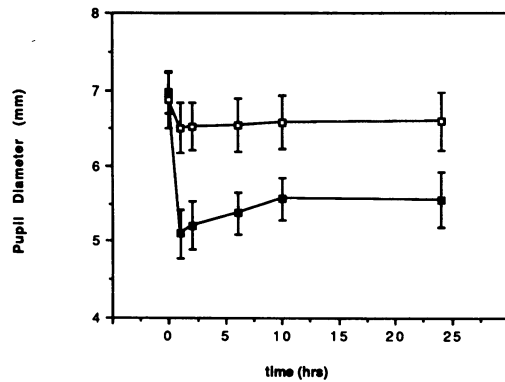


Figure 1 Mean pupil diameters (mm) with standard errors, for bunazosin 0.3% treated (closed symbols) and vehicle-only treated eyes (open symbols) following eyedrop instillation.

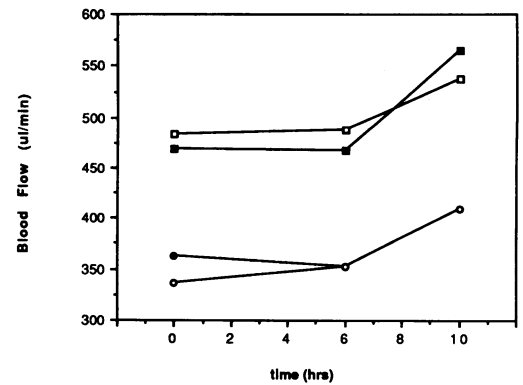


Figure 3 Mean values for pulsatile ocular blood flows ($\mu\text{l}/\text{min}$) in the erect (square symbols) and supine (round symbols) positions. Other symbols as in Figure 1.

position prior to eyedrop instillation and at 1, 2, 6, and 10 hours.

(4) Pulsatile ocular blood flow was calculated after measurement with a Langham pneumotonometeric system in the erect and, after 15 minutes, in the supine positions prior to eyedrop instillation and at 6 and 10 hours.

(5) Adverse responses to the drops (local burning, pain, misting of vision, headache) were sought by direct questioning prior to instillation and then at 1, 5, and 10 minutes and 1, 2, 6, 10, and 24 hours. At the same times tearing and redness of the eyes were assessed by inspection and the responses graded according to the scale: 0=none, 1=mild, 2=moderate, 3=severe.

(6) Heart rate and blood pressure were recorded by standard methods.

STATISTICAL ANALYSIS

Values for pupil diameter, palpebral height, intraocular pressure, and ocular blood flow were analysed by comparisons between the two eyes of each subject by Student's paired *t* test. The scaled measurements of ocular hyperaemia were ranked and subjected to a Wilcoxon signed rank test. Ocular discomfort and visual impairment, also recorded as discrete variables, were not analysed because so few positive responses were obtained.

Results

Pupil diameter. Mean pupil diameters are illus-

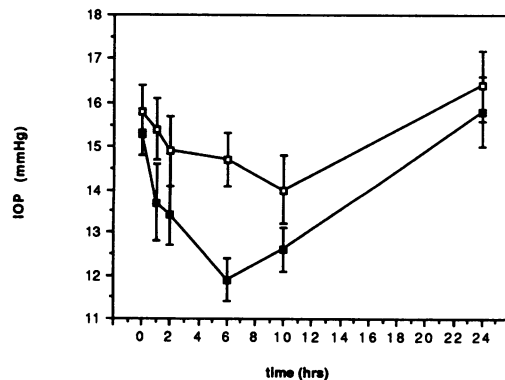


Figure 2 Mean Goldmann intraocular pressures (mmHg) with standard errors for bunazosin treated and vehicle-only treated eyes following eyedrop instillation. Symbols as in Figure 1.

trated in Figure 1. Miosis occurred in the drug-treated eyes and to a small extent in the untreated eyes. A significant drug effect ($p < 0.001$) was recorded from one hour to 24 hours after eyedrop instillation, but miosis was observed to persist in nine of 15 subjects for at least 48 hours.

Palpebral height. There was no significant change in palpebral height in either eye alone following eyedrop instillation. However, an interocular difference was detectable at 1 hour (0.7 mm mean, $p < 0.01$) and 2 hours (0.6 mm mean, $p < 0.01$) following treatment, demonstrating that bunazosin reduced palpebral height, causing a small degree of ptosis.

Intraocular pressure. The drug significantly reduced intraocular pressure (Fig 2). A small effect was noted after only 1 hour following instillation, but the greatest mean pressure difference between treated and untreated eyes occurred at 6 hours (2.7, SEM 0.5, mmHg, $p < 0.001$) as measured by Goldmann tonometry.

Pulsatile ocular blood flow. No significant changes in pulsatile flow were recorded as occurring either with time following eyedrop instillation or between treated and untreated eyes. There was a small increase in blood flow during the course of the day in both drug-treated and untreated eyes and in both erect and supine positions (Fig 3).

Symptoms and signs. Bunazosin-containing drops produced significantly more conjunctival hyperaemia than did the vehicle-only drops, the effect being greatest during the period 10 min to 2 h (Fig 4). Some residual effect was present at

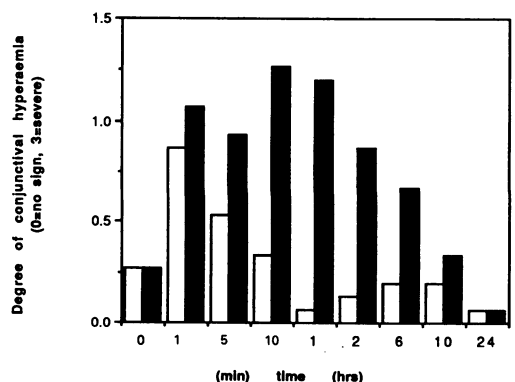


Figure 4 Mean values for degree of observed conjunctival hyperaemia, scaled as indicated in 'Methods,' for bunazosin treated (hatched bars) and vehicle-only treated eyes (open bars) following eyedrop instillation.

10 hours but had disappeared by 24 hours after eyedrop instillation.

Mild burning sensations were reported by 4/15 subjects, but any persistent sensation occurred equally between drug-treated and untreated eyes. Mild to moderate visual blurring was reported by 5/15 subjects, both eyes being equally affected.

Blood pressure and heart rate. No clear changes occurred in blood pressure during the course of the day. There was a small increase in the mean heart rate during the day in both the erect and supine positions, but in the presence of an almost unchanged blood pressure this was unlikely to be a drug effect.

Discussion

This study has shown that topical bunazosin 0.3% reduces intraocular pressure, though the effect was modest and rather less than that produced by topical β -adrenoceptor antagonists, which usually have a faster onset and greater magnitude of action. There were no significant changes in pulsatile ocular blood flow in this study, but the drug was administered only once. Future studies may show that longer term usage has greater effects on the ocular vasculature and produces important measurable changes.

No serious side effects nor adverse drug reactions were reported, but the drug did induce characteristic features of α -adrenoceptor blockade in the eye, comprising miosis, partial ptosis, and conjunctival hyperaemia. These cosmetic effects are likely to influence comp-

liance in clinical usage, but longer term studies in glaucoma patients are needed to find out if the magnitude of the ocular hypotensive action is sufficient to overcome this disadvantage.

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FIFTY YEARS AGO

The empty socket

It has often struck us as odd that one does not find an ophthalmological subject used as an Inn sign in this country, but we do not know of a single case. Other anatomical subjects occur: e.g., the hand often, the heart, occasionally. St. Peter's finger is met with in one instance. Arms are, of course, frequently found in this connexion, but here the significance is heraldic and not anatomical. The eye is very rarely met with in heraldry as we have observed before.

Care would be needed in giving an ophthalmic name to a pub, for if the house were called the 'evil eye' the more superstitious of the village inhabitants would give it a wide berth. And 'the squinting eye' would almost certainly become in local parlance the 'boss eye' and from that to 'boozy,' the transition is easy. Hardy would seem to have anticipated in a mild degree our

need, for one of the village inns in 'Tess' was called the 'Pure Drop.' We fear that in this case he was thinking of a drop of drink and not of an eye drop.

The late Mr George Pollock, in lecturing on fractures at St George's Hospital more than half a century ago, used to tell an apocryphal story of a certain publican who changed the name of his house from the 'crooked billet' to the 'crooked arm.' This was done to annoy the local doctor who had had a bad result in the treatment of a case of fracture in one of the publican's children. The results on the practice were said to have been disastrous and the doctor had to leave the district. Fortunately for us the eye hardly lends itself to such a theme. We suggest our heading as a possible sign for an inn in the hope that some eminent English artist may feel inclined to draw a portrait of the oldest inhabitant minus one eye.

Annotation in *Br J Ophthalmol* 1941; 25: 130–1.