Effects of long-term treatment with timolol on lacrimal gland function

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SUMMARY Thirty-two patients with raised intraocular pressure were treated for 1 year with topical timolol 0.5% twice daily. There was satisfactory pressure reduction on this drug alone in 25 patients. The tear flow (modified Schirmer I test) was measured, and the tear lysozyme concentration was assayed before, and at 3, 6, and 12 months after beginning treatment. No subjective symptoms occurred and no side effects were recorded. The tear flow and tear lysozyme concentration were not significantly reduced.

Timolol maleate (Timoptol) a β_1 and β_2 adrenergic receptor blocking drug, is widely used in the treatment of glaucoma.¹ Patient tolerance is good, largely because of the absence of local side effects.² Systemic absorption of the drug may, however, give rise to adverse cardiovascular, respiratory, and central nervous system reactions in susceptible patients.³ Few adverse ocular reactions to timolol have so far been reported, the more serious being sporadic reports of superficial punctate keratopathy and corneal anaesthesia.^{3,4} No prospective study has yet been carried out. The apparent lack of local anaesthetic activity (membrane-stabilising effect) with timolol compared with other beta-blocking drugs is one reason for its introduction for topical use.⁵

Severe adverse ocular reactions have been encountered in the past with the β_1 -selective blocking drug practolol.⁶ Patients who developed an oculomucocutaneous syndrome following its systemic administration were found to have decreased tear flow as well as a reduced concentration of tear lysozyme and IgA, indicating severe impairment of lacrimal gland function.⁶ A significantly reduced concentration of tear lysozyme was also found in patients who were taking practolol but whose eyes were clinically normal.⁷ It was therefore considered important that a critical prospective study be made of the effect of the long-term administration of timolol on lacrimal gland function. This paper reports our

findings, which contradict those of a recently published study that suggested timolol adversely affected lacrimal gland function.⁸

Patients and methods

Thirty-two patients of both sexes with newly diagnosed primary open-angle glaucoma (POAG) (23 patients, 44 eyes) or ocular hypertension (OH) requiring treatment (9 patients, 17 eyes) were included in the study. Their mean age was 61 years, range 20 to 79 years. All satisfied the following admission criteria: (1) no systemic disease contraindicating the use of beta-blocking drugs; (2) no external eye disease; (3) no existing topical ocular medication; (4) no concurrent treatment with systemic beta-blocking drugs or antibiotics.

Informed consent was obtained, and treatment was started with topical timolol 0.5% twice daily.

Slit-lamp examination of the external eye and measurement of tear flow and tear lysozyme concentration were carried out before beginning treatment with timolol and repeated after 3, 6, and 12 months. Assessment of intraocular pressure (IOP) control by applanation tonometry was carried out as frequently as deemed necessary and visual field examination after 6 and 12 months. An intraocular pressure of 21 mmHg or less (or minimal fall of 5 mmHg from the baseline IOP if 25 mmHg or less) was accepted as evidence of adequate control in those patients with primary open-angle glaucoma. For the ocular hypertensive patients an intraocular pressure of 24 mmHg

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or less (or a minimal fall of 5 mmHg from the baseline IOP if 28 mmHg or less) was accepted.

Tear flow was measured with Schirmer's strips in the unanaesthetised open eye. If wetting did not occur within 2 minutes the strip was removed and placed in another area of the lower fornix, and time counting was started again. This is a modification of the Schirmer I test.⁹ The length of wetted strip was recorded after 5 minutes. The maximum length was considered to be 30 mm.

Estimation of tear lysozyme concentration was carried out according to the method of Seal *et al.*,¹⁰ but the results were expressed in units per microlitre. Hen egg lysozyme standard was used, which had an activity of 24 300 units per milligram. Tear samples were collected 5 minutes prior to the Schirmer's test on 5 mm filter paper discs placed in the lower fornix. The discs were weighed in their bottles on a portable Cahn electronic balance before and after collection to give the weight, and hence volume, of the tear fluid collected. A known volume of eluting fluid was then added to the disc in its bottle prior to transport to the assay laboratory, where it was stored at -20°C .

Results

All 32 patients tolerated timolol well and no subjective side effects were recorded. No abnormality of the tear film, conjunctiva, or cornea was detected on slit-lamp examination in any patient during the 12-month study. Additional medication to control the IOP was required in 7 patients (13 eyes). Six patients (11 eyes) were adequately controlled by the addition of pilocarpine alone and were kept in the study. One patient required drainage surgery and was removed from the study after 5 months. One female patient, aged 77, with primary open-angle glaucoma, died 11 months after starting treatment with timolol.

The results of the modified Schirmer I tests and tear lysozyme estimations are given in Table 1. There was no significant difference between the mean values of the Schirmer I tests after 3, 6, and 12 months of

Table 2 Mean intraocular pressure in eyes treated with timolol alone

	Primary open-angle glaucoma		Ocular hypertension		All eyes	
	n	IOP mmHg	n	IOP mmHg	n	IOP mmHg
Pretreatment	44	28.7 (6.2)	17	29.5 (3.4)	61	28.9 (5.6)
At 2 weeks	44	17.8 (3.4)	17	20.5 (2.9)	61	18.6 (3.5)
At 3 months	39	18.3 (3.1)	17	21.1 (2.5)	56	19.1 (3.2)
At 6 months	37	17.6 (2.7)	17	20.4 (2.2)	54	18.5 (2.8)
At 12 months	31	17.0 (2.6)	17	21.2 (4.5)	48	18.3 (3.6)

n=Number of eyes. Standard deviation shown in parentheses.

topical timolol therapy when compared with the values before treatment was started. There was also no significant difference between the mean values of the tear lysozyme concentrations, at similar periods after starting timolol therapy, when compared with the pretreatment values, although the mean concentrations fluctuated within the limits of the normal range at 6 and 12 months.

The results of pressure lowering by timolol are given in Table 2. Adequate control of IOP by timolol alone was achieved in 70% (31 out of 44) of eyes with POAG over the 12 month period. Acceptable IOP lowering was achieved in all eyes with OH until the end of the 12 month period, when the IOP was found to be above 24 mmHg in 3 eyes.

Discussion

The lacrimal gland has a dual innervation—sympathetic and parasympathetic. The sympathetic nerve supply is from the superior cervical ganglion through the carotid plexus, and within the lacrimal gland there is a fine network of adrenergic fibres running between the secretory acini.¹¹ The role of the sympathetic is not fully understood, but Whitwell found that the injection of adrenaline into the gland stimulated secretion in the denervated human lacrimal gland.¹²

In a recent study¹³ it has been shown that the sympathetic plays a dominant role in the control of lacrimal protein secretion. Beta-receptors have been demonstrated on the acinar cells of the rabbit lacrimal gland,¹⁴ and blockage of these receptors has been shown to partially inhibit protein secretion in response to adrenergic stimulation.¹³ Antibacterial proteins present in tear fluid include IgA, IgG, complement, lysozyme, lactoferrin, and caeruloplasmin.^{15 16}

We have found no significant reduction in tear flow or in tear lysozyme concentration in our patients on topical timolol 0.5% twice daily. These findings contradict those of Bonomi *et al.*,⁸ who recorded a

Table 1 Results of mean values of Schirmer tests and tear lysozyme concentrations

Test	Patients before treatment		Patients using 0.5% timolol drops		
			After 3 months	After 6 months	After 12 months
Schirmer I (modified)	Right	23 (8)	22 (9)	22 (9)	23 (9)
	Left	21 (9)	20 (8)	22 (9)	23 (9)
Tear lysozyme concentration (units/ μl)	Right	126 (38)	129 (50)	144 (39)	107 (25)
	Left	127 (40)	121 (47)	146 (47)	109 (24)

Standard deviation shown in parentheses.

significant reduction ($p < 0.01$) in tear flow and lysozyme concentration in 30 patients with open-angle glaucoma at 7 and 45 days after treatment with topical timolol 0.25% twice daily. They did not, however, find a reduction in IgA which might be expected if the lysozyme concentration was reduced.⁶ We found timolol was well tolerated in our patients and associated with no subjective symptoms. The therapeutic effectiveness of timolol in lowering IOP was also confirmed.

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