

Interaction of timolol and adrenaline

ARNE ÖHRSTRÖM AND ÖRJAN KÄTTSTRÖM

From the Department of Ophthalmology of Malmö University of Lund, and the Department of Ophthalmology, Central Hospital, Västerås, Sweden

SUMMARY In a prospective double-blind randomised trial the interaction of timolol and adrenaline was studied in 20 patients with open-angle glaucoma and exfoliative glaucoma. After pretreatment for at least 2 weeks with timolol eyedrops adrenaline was added in a double-blind manner, and the intraocular pressure was recorded during 4 days. The study showed a significantly additive hypotensive effect of adrenaline, which was more pronounced in patients with exfoliative glaucoma.

Recently there has been a growing interest in beta-blockers in the treatment of glaucoma. Since the introduction of timolol maleate eyedrops this treatment is being used increasingly either alone or in combination with other antiglaucomatous drugs.¹ Timolol has been found to have a synergistic effect with most antiglaucomatous drugs.¹⁻⁴ However, conflicting results exist on the interaction of adrenaline and timolol. Results from open clinical trials indicate that the combination offers no advantage, while others have suggested an additive hypotensive effect.⁵⁻¹⁰ The present investigation was performed to evaluate the effect of adding adrenaline to patients already on timolol.

Material and methods

The study was carried out on 10 patients with open-angle glaucoma and 10 patients with exfoliation glaucoma. All 20 patients had pathological cupping of the disc and visual field defects. Informed consent was obtained according to the Helsinki-Tokyo convention. It was considered unethical to do a double-blind study including both drugs, which would leave

the affected eye sometimes without treatment and thus increase the risk of worsening the disease. To avoid this risk the study was designed as follows. Every patient received 0.5% timolol maleate 1 drop twice a day in each affected eye. The treatment was started at least 2 weeks before the trial. No other treatment was used. After at least 2 weeks the patient was admitted to hospital, and with continued treatment the intraocular pressure (IOP) was measured 4 times each day and the pupil size was noted twice a day (Fig. 1). Timolol was given at 7.00 a.m. and 7.00 p.m. and the test drug 5 minutes later. Timolol was given first so that the adrenaline-induced vasoconstriction would not interfere with the absorption of the drug. The intraocular pressure was measured by a calibrated Goldmann applanation tonometer at 8.00 a.m., 12.00 a.m., 4.00 p.m., and 8.00 p.m. The pupil size was determined at 8.00 a.m. and 4.00 p.m. with a Goldman projection perimeter in standard conditions of luminance.

Randomly in a double-blind manner on the 3rd and 4th day half the patients received twice a day an additional treatment of either 1% adrenaline eye drops (Eppy) or placebo (0.15 M NaCl solution). The same person made the recordings during the whole study. Thus at the end of the study we had 2

Correspondence to Dr A. Öhrström, Department of Ophthalmology, Köping Hospital S-731 01 Köping, Sweden.

Fig. 1 Treatment and recordings on the upper half illustrating the common treatment during 1 day of the trial, the lower half illustrating the additional treatment on the third and fourth day (IOP = intraocular pressure, PS = pupil size).

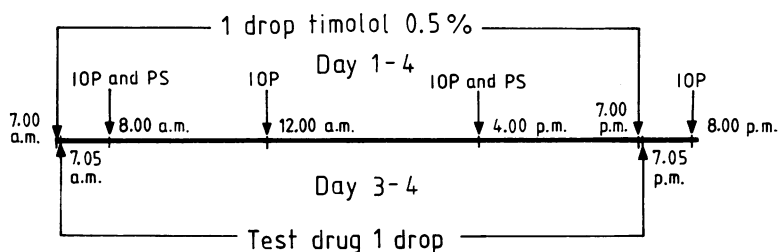


Table 1 Mean values of intraocular pressure (mmHg, \pm SD) on days 1+2 (control period) and on days 3+4 (combined treatment). n = number of recordings

	Glaucoma simplex, 10 patients		Exfoliation glaucoma, 10 patients	
	Day 1+2	Day 3+4	Day 1+2	Day 3+4
Adrenaline	20.875 \pm 3.280 n = 72 (9 eyes)	19.875 \pm 3.680	23.875 \pm 14.700 n = 48 (6 eyes)	17.833 \pm 6.501
Placebo	19.50 \pm 3.871 n = 72 (9 eyes)	20.875 \pm 4.838	25.812 \pm 12.084 n = 64 (8 eyes)	27.937 \pm 12.031

Table 2 Mean reduction of intraocular pressure (mmHg) during the 2 days of combined treatment (days 3+4) compared to the control period (days 1+2)

	Glaucoma simplex, 10 patients	Exfoliation glaucoma, 10 patients
	Mean reduction \pm SEM	Mean reduction \pm SEM
Adrenaline	-1.00 \pm 0.346 (9 eyes)	-6.042 \pm 0.577 (6 eyes)
Placebo	+1.375 \pm 0.346 (9 eyes)	+2.125 \pm 0.4997 (8 eyes)

groups both treated with timolol alone for the first 2 days and with timolol plus either adrenaline or placebo over the next 2 days.

The 10 patients with open-angle glaucoma (glaucoma simplex) were examined first. Five patients received adrenaline and 5 placebo as additional treatment, which resulted in 9 eyes in each group. Thereafter another group with 10 patients was studied, all having exfoliation glaucoma. As before the patients were divided into 2 groups of 5, and this resulted in 6 eyes receiving adrenaline and 8 placebo. The differences in tension in each eye between day 1 and 2 (control period) and day 3 and 4 (combined treatment period) were examined by Fisher's analysis of variance.

Results

INTRAOCULAR PRESSURE

The addition of adrenaline reduced the tension more in the exfoliative group ($P < 0.001$) than in the open-angle glaucoma group ($P < 0.01$) (Tables 1 and 2). The patients randomised to placebo showed in both groups a significant increase of tension, which we cannot explain. The difference between the adrenaline and placebo treatment was significant in both groups ($P < 0.001$).

PUPIL SIZE

An analysis of variance with regard to the differences between the control period day 1-2 and the combined treatment period showed no effect of placebo.

With the adrenaline combination the exfoliative group showed the strongest dilatation, 1.125 ± 0.173 mm (SEM) and the simplex group less 0.86 ± 0.468 mm (SEM), both with $P < 0.001$.

Discussion

The fact that an adrenergic agonist (adrenaline) and a beta-adrenergic receptor blocker (timolol) additively reduce intraocular pressure is surprising. One would expect they would antagonise each other.

An earlier report by Phillips *et al.*¹¹ with topical atenolol, another beta-blocker, and adrenaline in a 1-dose/1-day trial showed no additive effect of the combination, rather the reverse. Another report¹² of a 1-dose study on the interaction of atenolol and adrenaline showed a slight additive effect, but the effect was only significant 90 min after treatment. Earlier studies with healthy volunteers on the interaction of beta-blockers and adrenaline^{13,14} showed that with systemic propranolol and atenolol there was an additive hypotensive synergism. When the combination of topical timolol and adrenaline was studied in healthy volunteers during 2 periods of 3 days (double-blind cross-over randomised¹³) we found an antagonistic effect that eliminated the adrenaline-mediated effect. In that trial also timolol was given first.

In an open clinical study Boger *et al.*⁵ could not find any additional hypotensive effect of adrenaline in patients already receiving timolol eyedrops. However, other open clinical studies⁷⁻⁹ suggest an additive effect of this combination. Earlier double-blind cross-over investigations^{11,12} which showed an antagonistic or negligible effect of the topical beta-blockers and adrenaline combination were short-term trials (3 days and 1 day), with beta-blockers being started only on the first day of the trial.

In an open, cross-over study¹⁵ the addition of timolol to eyes pretreated for 1 week with adrenaline resulted in an additive hypotensive effect. On the other hand the addition of adrenaline after pretreatment with timolol showed a reduced hypotensive effect of adrenaline.

In this study, which shows an additive effect of

adrenaline and timolol drops, the treatment period with timolol drops was started at least 2 weeks, usually 3–4 weeks, before the investigation of the test drug. Other reports of long-term results of glaucoma treatment with timolol report a slowly diminishing effect.^{16–18} It is possible that after a longer period of treatment with timolol some kind of tolerance develops causing a less effective blocking of the beta-receptors. The contradictory results between short-term investigations and this study could be due to inefficient beta-receptor blockade at a later stage. Neufeldt *et al.*¹⁹ showed in rabbits that topical treatment for 4 days with timolol caused an increase in the density of beta-receptors in the eye, while treatment with adrenaline caused a decrease.

As Boger²⁰ showed, there is good evidence for alterations in the beta-adrenergic density in other organs during chronic systemic beta-adrenergic stimulation. This probable up-and-down regulation of the beta-receptor population, increasing with blockade and decreasing with stimulation, may be responsible for the long-term inefficacy of the beta-blockers or adrenaline.

This trial suggests that it is possible to combine topical treatment with timolol maleate and adrenaline eyedrops in glaucoma. The effects are not antagonistic, and the combination could be of value when miotics are undesirable, though the additional hypotensive effect is not prominent. As regards the effect on the pupil size, systemic and topical beta-blockers combined with adrenaline have an additive pupil-dilating action.^{9 13 14} Owing to the design of this study with patients on timolol during the whole trial it was not possible to confirm the additive pupil-dilating effect of timolol drops and adrenaline. The results showed, however, a highly significant dilatation of the pupil after adding adrenaline to the treatment with timolol. No significant effect was observed with placebo.

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A. Ohrström and O. Kättström

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