Dose response of oral timolol combined with adrenaline

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SUMMARY Oral timolol, a beta-adrenergic receptor blocker, was given in 5 different doses from 5 mg to 30 mg a day to 12 healthy volunteers in a double-blind cross-over trial. Adrenaline was instilled into one eye in each subject. Recordings of intraocular pressure during the trial suggested the presence of a dose-response relationship between the dose of timolol and the decrease of intraocular pressure. An analysis of the interaction of timolol and adrenaline showed that the adrenaline effect diminished linearly with increasing timolol dose, which finally made the combination less effective than timolol alone.

Most of the reports concerning the reduction of intraocular pressure by timolol maleate deal with topical timolol in clinical studies. To the best of our knowledge only one study reports on the reduction of intraocular pressure by oral timolol, and in that study only a single dose of 5 mg oral timolol was used. Thus the effects on intraocular pressure of systemically administered timolol have not been fully investigated. Earlier investigations have given contradictory results, suggesting both additive and antagonistic effects of combining timolol and adrenaline. As this combination avoids the disadvantages of miotics it could be a useful tool in the treatment of glaucoma. Earlier reports with oral beta-receptor blockers in the treatment of glaucoma have encouraged the use of this alternative oral treatment when carbonic anhydrase inhibitors are unsuitable.

However, there has been no dose-response study on the subject of systemically administered timolol. This study was designed to investigate the effect on intraocular pressure of different doses of oral timolol and also the effect of simultaneously administered adrenaline.

Material and methods

The study was approved by the Ethical Committee of the Central Hospital Västerås, and followed the guidelines of the Tokyo-Helsinki convention. The trial was of randomised, double-blind, cross-over design (Fig. 1). Twelve volunteers, all females, age range 18 to 50 years, participated in the study. Timolol maleate tablets in 5 different strengths (2.5, 5, 7.5, 10, and 15 mg) were dispensed by the local pharmacy. Lactose was used in the placebo tablets. Adrenaline borate 1% eye drops (Eppy) and 0.9% saline as placebo drops were used to investigate the effect of adrenaline. One drop of placebo was instilled into one eye and one drop of adrenaline into the other, the distribution being randomised but balanced, so that 6 of the subjects received adrenaline in the right eye and the other 6 in the left.

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Fig. 1 Design of the trial. Recordings of intraocular pressure and drug administration.
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Table 1  Mean intraocular pressure ±SEM with different doses of timolol: 0.9% saline in one eye and 1% adrenaline in the other. ΔE-P decrease of intraocular pressure following adrenaline drops. Each figure represents the mean of 110 recordings.

<table>
<thead>
<tr>
<th>Oral dose</th>
<th>Topical treatment</th>
<th>n</th>
<th>ΔE-P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adrenaline drops (E)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo drops (P)</td>
<td></td>
<td></td>
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<tr>
<td>placebo</td>
<td>11.9±0.1661</td>
<td>12.7±0.1661</td>
<td>2×110</td>
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<tr>
<td>5 mg</td>
<td>10.12±0.172</td>
<td>10.22±0.172</td>
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</tr>
<tr>
<td>10 mg</td>
<td>10.40±0.161</td>
<td>10.43±0.161</td>
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</tr>
<tr>
<td>15 mg</td>
<td>9.90±0.1545</td>
<td>9.83±0.1545</td>
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</tr>
<tr>
<td>20 mg</td>
<td>9.8±0.1510</td>
<td>9.69±0.1510</td>
<td>2×110</td>
</tr>
<tr>
<td>30 mg</td>
<td>9.77±0.1415</td>
<td>9.54±0.1415</td>
<td>2×110</td>
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</tbody>
</table>

For each individual subject the adrenaline was instilled into the same eye throughout the trial. Six of the subjects were studied on Mondays and Tuesdays and the other 6 on Wednesdays and Thursdays. The trial was randomised, so that each subject received a different dose of timolol each week, and each week each dose was received by 2 subjects. At the start of the trial each subject was given one tablet at 7 p.m. The next day at 7 a.m. another tablet was given and at the same time the eye drops were instilled, one drop into each eye. From 8 a.m. the intraocular pressures were recorded 2 hourly until 4 p.m. (8 a.m., 10 a.m., 12 noon, 2 p.m. and 4 p.m.) with a calibrated Goldmann applanation tonometer, the recordings being made by the same investigator throughout the trial. At 1 p.m. one further drop of adrenaline and one of placebo were given. Another tablet was given at 7 p.m. and the whole procedure was repeated the following day.

The results were analysed by Fisher's analysis of variance.

**Results**

During the third week one of the subjects developed bradycardia (45 beats/min) and had to leave the study. Her dose of timolol was 10 mg a day. The other 11 subjects completed the trial without any complications. The statistical analysis was based on a total of 1320 recordings of intraocular pressure (IOP).

Oral timolol used alone decreased the intraocular pressure significantly, p<0.001 (Table 1 and Fig. 2). In the full analysis of variance including both eyes treated with placebo drops and adrenaline the contrasts between eyes (reaction of IOP) and between timolol doses were not statistically significant, showing no further lowering of the IOP with increasing timolol doses.

However, when the half of the material (Table 2) in which no adrenaline was applied was analysed (Table 3), an increase in timolol dose was followed by a decrease in IOP values (p<0.05), which suggests a tendency towards a dose-response relationship.

An individual analysis of IOP responses revealed that one of the subjects reacted with an increase of IOP after adrenaline. This increase was significant.

![Graph showing dose-response curve of oral timolol with 0.9% saline drops in one eye and 1% adrenaline in the other eye. Every point represents the mean of 110 recordings.](http://bjo.bmj.com/)

**Table 2** Timolol treatment without adrenaline, sum of recordings of IOP during day 1 and 2 (IOP totals) at different dose levels of timolol. Measurements in mmHg

<table>
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<tr>
<th>Dose: mg</th>
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<th>10</th>
<th>15</th>
<th>20</th>
<th>30</th>
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<td>Individual no.</td>
<td>IOP totals</td>
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<tr>
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<td>104</td>
<td>106</td>
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<tr>
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<td>1148</td>
<td>1082</td>
<td>1066</td>
<td>1050</td>
<td>5471</td>
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Fig. 2  Dose-response curve of oral timolol with 0.9% saline drops in one eye and 1% adrenaline in the other eye. Every point represents the mean of 110 recordings.
both with placebo tablets (p<0.01) and with different doses of timolol (p<0.001). This remarkable response prompted us to check this particular subject’s reaction in a trial of oral timolol and adrenaline performed one year previously. An analysis of variance showed (p<0.01) a significant inverse reaction to adrenaline in that trial also.

An analysis of the pure effect of adrenaline (placebo/placebo versus placebo/adrenaline) in the present trial would have shown, if the values of this particular subject had been excluded, that it usually caused a highly significant decrease of IOP (p<0.001). However, in order not to disturb the validity of the statistical analysis no values were excluded, and the tables thus include this inverse reaction.

When differences in IOP values were found between adrenaline- and placebo-treated eyes at the 5 dose levels of timolol, a linear correlation of the means emerged (Table 1, Fig. 3), which is suggestive of a gradual inhibition of the adrenaline effect with increasing timolol dose. An analysis of this correlation using the mean IOP differences gave p<0.001 by parametric methods and p<0.0083 by the non-parametric Kendall rank correlation test.

The statistical analysis showed no significant changes between the differences of tension in the eyes on different days. A slight heterogeneity was shown in the analysis of the importance of time of measurement and of the response of individual subjects, but no tendency could be shown.

**Discussion**

Several investigators have reported a dose-response relationship between the doses of oral beta blockers and the reduction of intraocular pressure (propranolol,7 bupranolol,8 timolol3). With topical treatment the relationship has been more thoroughly investigated (atenolol,7 timolol,9 metoprolol10), and Bonomi et al.11 compared 9 different beta blockers.

This study shows that oral timolol lowers intraocular pressure when compared with placebo. A dose-response relationship seems to exist, but after 5 mg the further decrements of pressure with increasing dose are very small. A similar result was found in another study on timolol,3 when 2 doses (5 mg and 20 mg) were used.

The interaction of beta blockers and adrenaline is controversial. Favourable results with topical timolol and adrenaline showing an additive IOP-reducing effect have been reported.4-15

With the combination of topical atenolol and adrenaline Rushton16 reported an additive hypotensive effect. Higgins and Brubaker17 found that adrenaline and topical timolol had an additive effect on inhibiting the formation of aqueous humour, but found no significant change in the IOP.

On the other hand Phillips et al.18 reported that the combination of local atenolol and adrenaline was less effective than atenolol alone, and Boger et al.19 could not find any additive hypotensive effect of adrenaline in patients already receiving timolol drops. Goldberg et al.20 reported that prior treatment with topical timolol for a week significantly diminished the reduction in IOP produced by adrenaline. In a

![Graph showing the differences in intraocular pressures between the eye treated with adrenaline and the eye treated with 0-9% saline with different oral doses of timolol.](image-url)
double-blind randomised cross-over study with healthy volunteers Ohrström and Pandolfi demonstrated an antagonistic effect between topical timolol and adrenaline.

With respect to oral beta blockers, randomised double-blind cross-over trials have demonstrated an additive hypotensive effect of the beta-blocker-adrenaline combination. In a prior trial with oral timolol, in which doses of 5 mg and 20 mg were used, an additive effect was observed with the lower dose but an antagonistic one with the higher.

The present study (Fig. 3) shows that the effect of adrenaline diminishes linearly as the timolol dose is increased and that this finally makes the combination less effective than timolol alone.

As beta blockers act by competitive inhibition, a high oral timolol dose should provide a greater degree of beta blockade than a low dose. The doses used in this trial (5 mg–30 mg a day) could be expected to produce a beta receptor blockade ranging from weak to strong. The dose-response curve (Fig. 2) indicates that after 5 mg the additional effect of increasing the dose is very small, which is in agreement with Wettrell’s observations on propranolol.

Unfortunately there is no dose-response study comparing the IOP effects of different oral beta blockers. A systemic comparison of the beta blockade potency ratio, based on the inhibition of isoprenaline-induced tachycardia, showed timolol to be 6 times more potent than propranolol. The timolol doses used in the present study should thus hypothetically correspond to doses of 30–180 mg propranolol a day. Wettrell analysed the dose response for propranolol in doses 20–80 mg daily in ocular hypertension and showed a clear dose-response relationship. The mean IOP reduction from 20 mg propranolol was about 15–25%, and each doubling of the dose produced a further decrease of about 3–5%. The reduction was greater in the group with higher initial tension, a fact that has been observed by others. In this study all the subjects were normotensive, with a mean baseline IOP of the untreated eye of 12.76±2.60 SD. After the smallest dose of timolol the pressure fell to values slightly over 10 mmHg. The episcleral venous pressure is probably only a few mmHg lower than this value, and thus a further suppression of the production of aqueous humour cannot possibly produce a lowering of the IOP, as it would then be below the episcleral venous pressure. Perhaps the dose-response curve would have had a different appearance if a sufficient number of ocular hypertensives had volunteered. Regrettably they did not.

The reduction of IOP by topical timolol has been shown by fluorophotometry to be due to a decreased formation of aqueous humour. In a fluorophotometric study Townsend and Brubaker showed that the immediate effect of adrenaline is to raise the facility of outflow and to increase the production of aqueous humour. A comparison between timolol and adrenaline shows that the IOP-reducing effect of topical timolol is significantly greater than that of adrenaline.

There is no reason to believe that the basic mechanism producing the reduction of IOP differs between oral or topical timolol. Earlier observations of additive effects with low timolol doses and antagonistic effects with high timolol doses, and the finding of this trial that increasing the timolol dose decreases the effect of adrenaline, can be explained if a low dose of timolol combined with adrenaline decreases aqueous humour production and increases the facility of outflow, while a high dose of timolol still produces a decrease of aqueous humour but blocks the adrenaline-mediated increase of facility. A similar theory is proposed by Thomas and Epstein based on a study of the interaction of topical timolol and adrenaline showing a transient additive effect. The simultaneous stimulation by adrenaline of aqueous humour production would explain why a high dose of timolol combined with adrenaline is less effective than timolol used alone.

Since the beginning of the last decade oral beta receptor blockers, usually propranolol, have been used in the treatment of glaucoma. This use of oral beta blockers is controversial and beyond the scope of the present discussion. However, when a patient with arterial hypertension and glaucoma needs treatment for both diseases, an oral beta blocker seems to be the drug of choice. The results of this study on healthy volunteers suggest that there are no benefits in using high doses of oral beta receptor blockers in the treatment of glaucoma.

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References
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A. Ohrström

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