Long-term hypotensive effect of atenolol 4% eyedrops

R. F. BRENKMAN
From the Department of Ophthalmology, University Hospital, Leiden, The Netherlands

SUMMARY The effect of long-term application of 4% atenolol eye drops has been studied in patients with either glaucoma or ocular hypertension. In some patients who show a good initial response the ocular hypotensive effect gradually wears off with long-term use. This pattern of response appears to be more frequent in patients with pretreatment intraocular pressures of 25 mmHg, or greater. In combination with atenolol miotics or adrenaline show an additive effect.

Phillips et al. (1967) published the first report of the ocular hypotensive effect of a beta-adrenergic blocking agent (propranolol). Subsequently several other compounds in this pharmacological class were studied, and a similar effect was found, examples being practolol, oxprenolol, and atenolol (Vale and Phillips, 1973; Stilma, 1977; Elliot et al., 1975; Wettrell and Pandolfi, 1975).

Although propranolol is effective after topical administration (Vale and Phillips, 1970), it is considered to be unsuitable for therapeutic use by this route because of local irritant and anaesthetic effects. Practolol was well tolerated on topical administration but has been withdrawn because of side effects reported after oral administration (Rahi et al., 1976).

The pharmacological profiles of the beta-adrenergic blocking agents differ considerably, and the only common property among those showing an ocular hypotensive effect is a β₁-blocking effect (Table 1). Atenolol is a cardioselective (β₁) blocking agent and is devoid of membrane stabilising and intrinsic sympathicomimetic effects. It is of interest that MacDonald et al. (1976) reported that atenolol produced a greater reduction in intraocular pressure than propranolol (a non-selective compound) on oral administration.

Table 1 The pharmacological properties of propranolol, practolol, and atenolol

<table>
<thead>
<tr>
<th>Material</th>
<th>β₁ + β₂ blockade</th>
<th>membrane stabilising effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Practolol (Eraldin)</td>
<td>β₁, blockade</td>
<td>little intrinsic sympathicomimetic activity</td>
</tr>
<tr>
<td>Atenolol (Tenormin)</td>
<td>β₁, blockade</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 The study group

<table>
<thead>
<tr>
<th>Material</th>
<th>16 patients (10 male, 6 female) in whom glaucoma had not previously been detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 29-80 years (mean 61 years)</td>
<td></td>
</tr>
<tr>
<td>Gonioscopic classification: wide angle 11</td>
<td>intermediate angle 5</td>
</tr>
<tr>
<td>narrow angle 0</td>
<td></td>
</tr>
</tbody>
</table>

(No special types of glaucoma)

Table 3 The 4 groups of patients classified according to their base-line pressure (Bip)

<table>
<thead>
<tr>
<th>Group I: Bip (base-line pressure) 20-25 mmHg; 8 patients (5 glaucoma suspect)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group II: Bip 25-30 mmHg; 4 patients</td>
</tr>
<tr>
<td>Group III: Bip 30-35 mmHg; 2 patients</td>
</tr>
<tr>
<td>Group IV: Bip 35-45 mmHg; 1 patient</td>
</tr>
</tbody>
</table>

The promising results of our single-dose study with 4% atenolol eyedrops (Brenkman, 1977) prompted us to investigate the ocular hypotensive effect of topical atenolol during long-term therapeutic use, either as sole therapy or in combination with miotic agents or adrenaline.

Patients and methods

The study group consisted of 16 previously untreated patients (Table 2). Five patients were classified as ocular hypertensives, the remainder as suffering from open- or intermediate-angle glaucoma. Base-line intraocular pressure levels were recorded on 3 or 4 occasions over a period of several weeks, and the average of these values was used to classify the patients into 4 subgroups (Table 3).
On the first day of atenolol treatment intraocular pressure was recorded for up to 7 hours after a single instillation (into both eyes) of 4% atenolol. Subsequently the patients were treated with 4% atenolol administered 3 times daily, and the intraocular pressure was recorded, 1, 2, 4, 8, and 16 weeks later.

If control of intraocular pressure was considered to be unsatisfactory on follow-up, atenolol was discontinued and alternative therapy instituted. In the majority of these cases the following sequence was followed until satisfactory control of intraocular pressure was regained:

1. Isoptocarpine 2%;
2. Isoptocarpine 2% + atenolol 4%;
3. Glaucodrine;
4. Glaucodrine + atenolol 4%;
5. Surgery.

The procedure is summarised in Fig. 1, and the criterion of control was an intraocular pressure of 21 mmHg or less.

![Fig. 1 Plan of our research](image)

**Fig. 1 Plan of our research**

![Fig. 2 Fall in intraocular pressure (IOP) after a single dose of atenolol 4% eyedrops (Blp = base-line pressure)](image)

**Fig. 2 Fall in intraocular pressure (IOP) after a single dose of atenolol 4% eyedrops (Blp = base-line pressure)**

![Fig. 3 Single dose response curve according to the 4 groups of patients](image)

**Fig. 3 Single dose response curve according to the 4 groups of patients**

![Fig. 4 Long-term hypotensive effect of atenolol 4% eyedrops according to the 4 groups of patients](image)

**Fig. 4 Long-term hypotensive effect of atenolol 4% eyedrops according to the 4 groups of patients**
Fig. 5a  Base-line pressure, single-dose curve, and follow-up of patient 18 (group I)

Fig. 5b  Base-line pressure, single-dose curve, and follow-up of patient 22 (group II)

Fig. 5c  Base-line pressure, single-dose curve, and follow-up of patient 20 (group III)

Fig. 5d  Base-line pressure, single-dose curve, and follow-up of patient 16 (group IV)
Fig. 6. Long-term hypotensive effect of atenolol 4% eyedrops alone, with regard to, and in combination with, isoptocarpine 2% and Glaucaadrine

Results

SINGLE-DOSE PHASE
The group mean intraocular pressure levels were calculated for the different time points, and the resulting day curve was compared with similar data from a previous single-dose study (Fig. 2).

The mean intraocular pressure reduction over the 7-hour follow-up period was 24% in this study, as compared to 25% in the previous study.

In Fig. 3 the single-dose day curves are subdivided according to the previously described pretreatment pressure classification, and the magnitude of the ocular hypotensive effect appears to be dependent on the base-line pressure, though the number of subjects in the higher-pressure groups is small.

MULTIPLE-DOSE PHASE
In the multiple-dose phase intraocular pressure was recorded at midday (i.e., 3 hours after the morning dose of atenolol), and the mean levels for the 4 subgroups are shown in Fig. 4.

It can be seen that the majority of patients in groups II–IV were withdrawn from treatment with atenolol after 2 to 4 weeks because of diminution of the initial response to the drug. In contrast the majority of patients in group I showed a sustained response to the drug over the 16-week follow-up period (1 patient only in this group was transferred to isoptocarpine after 4 weeks' therapy with atenolol). The responses of representative patients from each subgroup are shown in Figs. 5a to d.

After discontinuation of atenolol the progress of the treatment failures was monitored through the secondary treatment sequence. It is of interest that none of these patients showed a satisfactory response to isoptocarpine alone. At the time of preparation of this report 1 patient was controlled on combined therapy with isoptocarpine and atenolol, 2 on Glaucaadrine (2% aceclidine + 1% adrenaline) and atenolol, and 1 after glaucoma surgery. Two other patients had entered the sequence, but follow-up data were not yet available.

From analysis of the individual intraocular pressure curves an attempt was made to evaluate the relative efficacy of the different therapeutic regimens. This analysis is summarised in Fig. 6. It suggests that atenolol has an additive effect with miotic agents and possibly also with adrenaline. However, the number of patients involved is too small to permit a meaningful statistical evaluation.

Discussion
The discrepancy between the initial (single-dose) response to atenolol and the subsequent response on longer-term treatment, observed in a proportion of the patients in this study, requires further investigation because of the therapeutic implications. The results of this study indicated a relationship between high pretreatment intraocular pressure levels and subsequent loss of effect during atenolol treatment. Tachyphylaxis to beta-adrenergic agonists is well documented (Langham, 1975; Paterson and Paterson, 1971) but is not known to be related to the pre-treatment pressure level.

It is of interest that the patients who showed loss of effect to atenolol also appeared relatively resistant to established glaucoma therapy. It is not known, however, whether these patients showed a first-dose response to isoptocarpine or Glaucaadrine. This aspect of primary or secondary treatment failure should be carefully defined wherever feasible.

Conclusions
A single administration of atenolol 4% eyedrops produces an unequivocal reduction in intraocular pressure, with a maximum effect occurring between 3 and 5 hours after instillation. In a proportion of patients the ocular hypotensive effect diminishes over the next few weeks. The presence of pretreatment intraocular pressure in excess of 25 mmHg appears to predispose to this occurrence. Atenolol produces an additional ocular hypotensive effect when co-administered with adrenaline and/or miotic therapy.

Atenolol eyedrops were kindly supplied by ICI Pharmaceuticals Ltd. We are grateful to Dr W. J. van Zijl and Dr A. Rushton for information and discussion.

References
Long-term hypotensive effect of atenolol 4% eyedrops


