Long-term hypotensive effect of atenolol 4% eyedrops

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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 Practolol was well tolerated on topical administration but has been withdrawn because of side effects reported after oral administration (Rahi et al., 1976).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 β₂-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>
<thead>
<tr>
<th>Table 1</th>
<th>The pharmacological properties of propranolol, practolol, and atenolol</th>
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</thead>
<tbody>
<tr>
<td>Propranolol (Inderal)</td>
<td>β₁ + β₂ blockade, membrane stabilising effect</td>
</tr>
<tr>
<td>Practolol (Eraldin)</td>
<td>β₂, blockade, little intrinsic sympathicomimetic activity</td>
</tr>
<tr>
<td>Atenolol (Tenormin)</td>
<td>β₁, blockade</td>
</tr>
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</table>

Table 2  The study group

<table>
<thead>
<tr>
<th>Material</th>
<th></th>
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<tbody>
<tr>
<td>16 patients (10 male, 6 female) in whom glaucoma had not previously been detected</td>
<td></td>
</tr>
<tr>
<td>Age 29-80 years (mean 61 years)</td>
<td></td>
</tr>
<tr>
<td>Gonioscopic classification:</td>
<td></td>
</tr>
<tr>
<td>wide angle</td>
<td>11</td>
</tr>
<tr>
<td>intermediate angle</td>
<td>5</td>
</tr>
<tr>
<td>narrow angle</td>
<td>0</td>
</tr>
<tr>
<td>(No special types of glaucoma)</td>
<td></td>
</tr>
</tbody>
</table>

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

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

![Graphic showing the plan of the research with different treatment groups and outcomes]

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

![Graph showing the fall in IOP after a single dose]

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

![Graph showing the single dose response curve with different groups and outcomes]

**Fig. 4 Long-term hypotensive effect of atenolol 4% eyedrops according to the 4 groups of patients**

![Graph showing the long-term hypotensive effect with different groups and outcomes]
Therapy: Atenolol 4% 3dd

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)
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 pretreatment 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 Glaucadrine. 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.

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References


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