Atenolol versus adrenaline eye drops and an evaluation of these two combined

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SUMMARY In a 1-day, 1-dose, double-masked, randomised trial, with each of 12 patients acting as his/her own control, atenolol drops 4% (a selective β₁-adrenergic blocker) produced a significantly greater fall in ocular tension measured by applanation than did adrenaline drops 1% (P<0.01 Wilcoxon matched pairs signed ranks test). The mean differences, which favoured atenolol, between the falls in pressure produced by these 2 drugs at 1·5 hours, 3·5 hours, 5·5 hours, and 7 hours after instillation of the drops was 2·1, 4·6, 4·0, and 3·6 mmHg, respectively. Long-term studies would be required before any conclusion was justified about the relative merits of these 2 drugs in the treatment of glaucoma.

There was no significant difference between the ocular hypotensive effects of atenolol-thendrenaline and adrenaline-then-atenolol. It was disappointing that the expected adjuvant effect of atenolol’s preceding adrenaline was not found—rather the reverse. Atenolol alone, however, was significantly better than atenolol-then-adrenaline (P<0.02 Wilcoxon matched pairs signed ranks test), and there was also some indication that it was superior to adrenaline-then-atenolol. The response to adrenaline did not differ markedly from the response to the combination in either order.

It is now well established that β-adrenergic blocking drugs administered systemically reduce ocular tension (Phillips et al., 1967; Coté and Drance, 1968; Vale and Phillips, 1970, 1973; Sharaf et al., 1974; Wettrell and Pandolfi, 1975; Elliott et al., 1975). Administered as eye drops they also have an ocular hypotensive effect (Musini et al., 1971; Vale et al., 1972; Vale and Phillips, 1973; Bonomi and Steindler, 1975; Phillips et al., 1976, 1977; Wettrell and Pandolfi, 1977; Zimmerman and Kaufman, 1977a, b).

The selective β₁-adrenergic blocker atenolol (Phillips et al., 1976, 1977; Wettrell and Pandolfi, 1977), and the β₁- and β₂-blocker timolol maleate (Zimmerman and Kaufman, 1977a, b) administered as eye drops have no local anaesthetic effect and so can be seriously considered as potential topical therapy in the glaucomas, subject to the results of long-term trials. An advantage is that they have no effect on pupil or accommodation.

A comparison of the potency of each of these against standard remedies such as pilocarpine and adrenaline and, of course, against each other would be of considerable interest. Also, in glaucoma treatment these drugs alone are probably unlikely to be powerful enough, so that their effect in combination with other established drugs is worth studying. Possibly the most theoretically interesting first drug for comparison, and also for study as a combinatorial, would be the traditional adrenaline drops 1%.

Adrenaline (epinephrine) eye drops have an established place in the treatment of chronic simple glaucoma (noradrenaline also reduces ocular tension), which seems to result from a decrease in production of aqueous humour and an increased outflow (Duke-Elder, 1969).

Aim of investigation

One question is posed and one hypothesis is tested in this investigation.

The question: Is there a significant difference between the ocular hypotensive effect of atenolol drops 4% and adrenaline drops 1%?

The hypothesis: Adrenaline drops (α, β₁, and β₂ stimulator) reduce ocular tension, yet atenolol, which is a selective β₁-adrenergic blocker, also
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Atenolol (Tenormin) 4% eye drops were supplied as clinical trial material by ICI (Pharmaceuticals) Ltd. Eppy 1% (Smith & Nephew) (adrenaline 1% BP) was obtained through the hospital pharmacy.

Twelve patients were admitted to the trial after giving their informed consent. Their diagnoses, pretrial, and intertest treatments are recorded in Table 1. Six had bilateral quite symmetrical open-angle glaucoma (OAG), 1 had asymmetrical open-angle glaucoma, and 2 had unilateral open-angle glaucoma (1 'pigmentary' and 1 with pseudoxefoliation on lens capsule). Three had closed-angle glaucoma (CAG) with iridectomies in 5 eyes and an iris inclusion in 1 eye; only 1 eye was 'normal'(with peripheral iridectomy), 1 had borderline chronic CAG, and 4 had chronic CAG, though without markedly raised pressures.

Method

CLINICAL
Each patient attended on 2 occasions for the atenolol versus adrenaline comparison, and on 2 other occasions for the comparison between atenolol-then-adrenaline and adrenaline-then-atenolol. There was an interval of 1 week between test days for 9 patients and an interval of 3 or 4 days for 3 patients.

On each test day applanation tonometry was done first on the right eye and then on the left at 09.00, 10.30, 14.30, and 16.00 h, after Ophthaine (proparacaine HCl) 0.5% eye drops as topical anaesthetic. The same tonometrist (PMG) did all applanation tonometries on all patients except 1; in that case the usual tonometrist could not be available, so that all tonometries were done by another experienced technician. The tonometrist was unaware of the treatment which had been instilled (see below). The applanation tonometer was recalibrated every 2 weeks.

Immediately after the 09.00 h reference tonometry test drops were instilled (first instillation), followed 30 minutes later by different drops (second instillation).

In the comparison atenolol-then-adrenaline versus adrenaline-then-atenolol the test preparations were of course atenolol drops 4% and Eppy drops 1% (adrenaline 1% BP). The same drops were used as first instillation in the comparison atenolol versus adrenaline in each case were followed 30 minutes later by saline drops 0.9%. Thus patient and tonometrist could not distinguish the 4 test days, but unusual taste might suggest 'active' drops (saling drops and atenolol drops produce the same ocular discomfort, that is, negligible).

Although the label which designated the bottle's contents was obscured by another which stated only the patient's name and specified the test day and the order of instillation (first or second), it was possible to deduce the bottle's contents from the shape or stopper. We decided not to risk inactivation of adrenaline by decanting it into a standard bottle, and so a separate technician instilled the treatment, the tonometrist thereby remaining 'masked'. A disposable dropper was used for each instillation in order to achieve a standard volume.

All antiglaucoma medication was stopped 36 hours before each test day. Between test days patients continued their usual treatment.

The order in which the 4 pairs of treatments (atenolol-then-adrenaline, adrenaline-then-atenolol, atenolol-then-saline, and adrenaline-then-saline) were given was decided by a Latin square design, chosen to balance the residual effect of previous test treatment as well as to allow for any tendency in diurnal pressure variations to change with time. Patients entered the trial in 3 blocks of 4 patients each. The complete design is shown in Table 2.

The order of paired treatments so decided for each of the 12 patients was written on slips of paper. The 4 slips for each patient were placed in an envelope, which remained sealed until a patient entered the trial, when the seal was broken and the series of bottles for that patient were labelled.

No vehicle (or placebo) day has been included in order to minimise the number of patients required to maintain a balanced design and also to avoid the need for patients to attend for a fifth test day.

STATISTICAL
In the planning of the experiment it was considered that a difference of 3 mmHg or more would be important in the atenolol versus adrenaline study. Twelve patients were necessary to provide data which, on analysis, would be powerful enough (power: at least 80%) to detect that difference at a significant level (P<0.05). Calculation of trial size was based...
on historical data from controlled studies at the Princess Alexandra Eye Pavilion. This prior information suggested that differences were distributed with variance of 12 mmHg$^2$. The anticipated difference due to order of administration atenolol-then-adrenaline versus adrenaline-then-atenolol was assumed to be less than 3 mmHg, so that our chance of detecting it with 12 patients was therefore less. (To detect a difference of 2 mmHg with power 80% would require 24 patients; a difference of 1 mmHg 96 patients.)

For each patient the pressure change (compared with the 09.00 h reference pressure) at 10.30, 12.30, 14.30, and 16.00 h has been calculated. For patients with symmetrical glaucoma (Nos. 1, 5, 6 to 12) the mean R and L change in pressure has been used, that is, pressure change at time, t, has been defined as:

$$(09.00 \text{ h pressure in R} - \text{pressure at time, t, in R}) + (09.00 \text{ h pressure in L} - \text{pressure at time, t, in L})$$

For the patients with unilateral or asymmetrical glaucoma (Nos. 2, 3, and 4) pressure change at time, t, is defined as: 09.00 h pressure in more glaucomatous eye minus pressure at time, t, in more glaucomatous eye.

As a basis for the statistical analysis, we have calculated overall pressure fall, which summarises observations at the 4 times 10.30, 12.30, 14.30, and 16.00 h and is defined as:

$$(\text{pressure fall at 10.30} + \text{pressure fall at 12.30} + \text{pressure fall at 14.30} + \text{pressure fall at 16.00})$$

This gives effectively equal weight to the 4 applanation readings. Mean and median difference between overall pressure falls for atenolol 4%, and for adrenaline 1% were then calculated and the odds assessed against chance as the explanation for any discrepancy between them and zero, the latter being expected from the null hypothesis that atenolol 4% and adrenaline 1% are equally effective in reducing ocular tension.

Results

Part 1

Fig. 1 presents a scattergram of the difference between (a) pressure fall on atenolol and (b) pressure fall on adrenaline. Note that there is a wider scatter as interval following administration increases. Inspection of this scattergram strongly suggests that atenolol 4% is a more powerful ocular hypotensive agent than adrenaline 1%. The overall pressure fall (see 'Method' and Fig. 2) is significantly greater after atenolol drops 4% than after Eppy drops 1% (P<0.01, Wilcoxon matched pairs signed ranks test). Median difference in overall pressure fall was 2.3 mmHg (mean difference 3.6 mmHg). The variance has been estimated as 11.8 mmHg$^2$, in close agreement with our prior information, but in the analysis a normal distribution of the difference has not been assumed.

Might a chance difference in the 09.00 h reference pressure favour the atenolol day? Fig. 3 shows that there is little difference between reference pressures on these 2 test days and there is no consistent bias towards 1 drug.

We plotted the overall pressure fall against the logarithm of the 09.00 h reference pressure. In the case of atenolol, the former increased linearly with the latter, whereas in the case of adrenaline there was only a slight indication of linearity.

Part 2

It was disappointing to find no significant difference between overall pressure falls produced by atenolol-then-adrenaline, compared with falls produced by adrenaline-then-atenolol. Furthermore, no adjuvant effect has been observed, rather the reverse. Atenolol alone, however, was significantly better than atenolol followed by adrenaline (P<0.02, Wilcoxon matched pairs signed ranks test), and there was also some indication that it was superior to adrenaline followed by atenolol (Fig. 4). Response to adrenaline alone did not differ markedly from the response to atenolol-then-adrenaline or adrenaline-then-atenolol.

Discussion

This study related only to a 1-day and 1-dose double-masked carefully randomised trial so that no conclusions can be made about long-term treatment during which the effect of continued atenolol and adrenaline might decline. That is, without long-term studies we cannot claim that atenolol should replace adrenaline.

After the start of the trial it was realised that a possible bias existed in favour of atenolol as an ocular hypotensive agent to the detriment of adrenaline. Patients had often had long-continued treatment with adrenaline before the trial, but none of the early cases of course had had atenolol. Tolerance to adrenaline in spite of 36 hours' withdrawal...
Table 1

<table>
<thead>
<tr>
<th>Serial No.</th>
<th>Diagnosis</th>
<th>Pre- and intertest treatment (stopped 30 hours before test days)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R OAG L OAG</td>
<td>R and L pilocarpine 2% thrice daily pilocarpine 4% at night</td>
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</tr>
<tr>
<td>2</td>
<td>R OAG (pseudo-exfoliation) L normal</td>
<td>R pilo. 4%, four times daily R adrenaline 1% twice daily L nil</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>R normal L OAG ('pigment-ary')</td>
<td>R nil L pilo. 2%, thrice daily L pilo. 4% at night</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>R normal L chronic CAG</td>
<td>R nil L adrenaline 1% twice daily L iris inclusion 18 months before test period</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>R OAG L OAG</td>
<td>R and L pilo 2%, thrice daily pilo. 4% at night adrenaline 1% at night</td>
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</tr>
<tr>
<td>6</td>
<td>R OAG L OAG</td>
<td>R and L pilo. 4%, four times daily adrenaline 1% twice daily</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>R OAG L OAG</td>
<td>R and L pilo. 2%, thrice daily pilo. 4% at night</td>
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<tr>
<td>8</td>
<td>R OAG L OAG</td>
<td>R and L pilo. 2%, thrice daily pilo. 4% at night adrenaline 1% twice daily atenolol 4% thrice daily</td>
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</tr>
<tr>
<td>9</td>
<td>R chronic CAG L chronic CAG</td>
<td>R pilo. 4%, four times daily L pilo. 4%, four times daily</td>
<td>R and L sector iridectomies for acute CAG following iridocyclitis 3 years before tests</td>
</tr>
<tr>
<td>10</td>
<td>R chronic CAG L chronic CAG</td>
<td>R and L atenolol 4% thrice daily adrenaline 1% twice daily pilo. 2%, four times daily</td>
<td>R and L sector iridectomies 3 years before tests</td>
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<tr>
<td>11</td>
<td>R OAG L OAG</td>
<td>R and L pilo. 1%, thrice daily pilo. 2% at night</td>
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</tr>
<tr>
<td>12</td>
<td>R OAG L ? early OAG</td>
<td>R pilo. 1%, twice daily L nil</td>
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</tr>
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</table>

OAG = open-angle glaucoma. CAG = closed-angle glaucoma.

Table 2

<table>
<thead>
<tr>
<th>Block</th>
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<th>3</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Study day</td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>Aa A aA a a aA A a a A A a A a A a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>A a A aA aA Aa A a a A A a A a A a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>aA Aa a A A a aA A a a A a A a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>a aA A aA aA A a a aA A a A a</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A = Atenolol, a = Adrenaline. aA = Atenolol followed by adrenaline. Aa = adrenaline followed by atenolol.

Fig. 1 Scattergram of pressure fall due to atenolol minus pressure fall due to adrenaline shows highly consistent advantage to atenolol with increasing scatter towards the late afternoon. 'Pressure fall' implies subtraction of applanation readings at 10.30, etc., from the pretreatment reference pressure at 09.00 which was followed (in randomised order) by instillation of atenolol 4% on one day and adrenaline 1% on another.
might well cause a poorer response to that drug than would be observed in an eye previously unexposed to adrenaline. However, in fact some patients had never previously had adrenaline (Nos. 1, 3, 7, 9, 11, 12). In order to achieve greater equality in later patients atenolol drops 4% 3 times a day were prescribed for about a month so that their eyes would not be completely fresh to the drug.

Fig. 2 Difference in 'overall' pressure fall: atenolol minus adrenaline. 'Overall' implies averaged difference between applanation pressure at 10.30, 12.30, 14.30, and 16.00, and the 09.00 h pressure, i.e., summed differences divided by 4. Note that in only 1 case was adrenaline superior to atenolol. The median difference, 2.3 mmHg, was significantly different from zero (P < 0.01: Wilcoxon matched pairs signed ranks test). The mean difference was 3.6 mmHg

- Patients neither treated by atenolol nor adrenaline previously.
- Patients previously treated by pilocarpine, adrenaline, and atenolol.
- Patients previously treated by adrenaline, not atenolol (i.e., possibly biased in favour of atenolol)

\( \text{u} = \text{Unilateral or asymmetric glaucoma.} \\
\text{I = Closed-angle glaucoma with iridectomy.} \\
\text{II = Closed-angle glaucoma with iridectomy.} \)

Fig. 3 Graph to show that there was no systematic tendency for the 09.00 h pressure to be consistently low or high on atenolol day compared with adrenaline day

Atenolol - adrenaline, atenolol

\[ \text{Mean difference } = 1.7 \text{ mmHg} \]

\[ \text{Median difference } = 1.2 \text{ mmHg} \]

Atenolol - atenolol, adrenaline

\[ \text{Mean difference } = 2.8 \text{ mmHg} \]

\[ \text{Median difference } = 2.5 \text{ mmHg} \]

Fig. 4 Differences in overall pressure fall on different treatments compared. Only the atenolol minus atenolol-then-adrenaline difference was significant (P < 0.02, Wilcoxon matched pair signed ranks test), but atenolol alone may also be superior to adrenaline-then-atenolol. The other differences (atenolol-then-adrenaline minus adrenaline-then-atenolol; adrenaline minus adrenaline-then-atenolol; adrenaline minus atenolol-then-adrenaline) were not significant

\( \times = \) Possibly biased in favour of atenolol because pre- and inter-test treatment included adrenaline but not atenolol.

Inspection of Fig. 2 (see key) suggests, however, that this possible objection to the validity of our conclusions is not substantial.

The mode of action of the \( \beta \)-blockers is just as unknown as that of adrenaline. Because of the relatively greater potency systemically (Elliot et al., 1975) than topically (Phillips et al., 1976, 1977) an effect on production of aqueous humour was suggested. In the case of timolol maleate (a \( \beta_1 \) and \( \beta_2 \) blocker), which has presumably a similar mode of action, there is some evidence from tonography that it reduces production of aqueous humour (Zimmerman et al., 1977).

Ideally, new patients with open-angle glaucoma and high ocular tension who had never been previously treated should have been used in this study; such a group would have taken very many months to accumulate. Most of our presently reported patients do not have high pressures, so that we suspect that the differences we have observed may underestimate the situation which would occur in open-angle glaucoma. Also it was a small disadvantage of this group that 2 patients with unilateral glaucoma and 3 others with closed-angle glaucoma (operated on) were included, but it is interesting that the latter cases showed falls in pressure.

The simplifying second hypothesis tested in this investigation received no support. The recent observation that a \( \beta_1 \) and \( \beta_2 \) blocker, timolol maleate, reduces ocular tension (Zimmerman and Kaufman, 1977a, b) also tends to detract from it, as does the observation that salbutamol, a \( \beta_2 \) stimulator, also reduces ocular tension (Paterson and Paterson,
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1971). Although we are as ignorant of the mechanism of action of the β blockers as we are of adrenergic agonists, these drugs can still be considered for use in the treatment of glaucoma, subject to long-term studies of effectiveness and toxicity.

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References


