Dose response for blood pressure and degree of cardiac β-blockade with atenolol

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Summary
The hypotensive effect of 25 mg, 50 mg, 75 mg, 100 mg and 0 mg of atenolol daily were compared in a double-blind within-patient study. The fall in blood pressure with 25 mg daily was not significantly different than with 100 mg. The dose response curve lies between 0 and 25 mg daily. Cardiac β-blockade (measured by suppression of exercise tachycardia) was not maximal with 25 mg of atenolol daily. The dose response curves for β-blockade and the hypotensive effect are not parallel.

Introduction
Several studies have shown that a dose of 100 mg atenolol daily is effective in lowering blood pressure in hypertensive patients (Marshall, Barritt and Harry, 1977). Increasing the daily dose to 200 or 400 mg daily does not usually lower pressure further. Petrie et al. (1977) found 50 mg to be as effective as 100 mg. It is of interest to establish the shape of the dose response curve and for this reason the present authors have studied the effect of the smallest dose of atenolol that they could obtain. It was further hoped that the data would cast light on the little explored subject of the relationship between hypotensive effect and degree of β-blockade as measured by suppression of exercise tachycardia. As expected, suppression of heart rate proved to be a marker of compliance to tablet taking throughout the study.

Patients and methods
Ten patients, 6 men and 4 women were studied. Their age range was 40–56 years, mean 49 years. All had essential hypertension and had previously been shown to attain an adequate fall in blood pressure when treated with 100 mg atenolol once daily. Atenolol was withdrawn 4 weeks before entry into the run-in part of the trial. They were receiving no other treatment.

A placebo tablet was given during the 4 weeks run-in and the washout periods of 2 weeks between doses of atenolol. In a double-blind fashion according to a Latin Square design, 25, 50, 75, 100, and 0 mg of atenolol were each given for 4 weeks. All doses were given in an identical tablet taken in the morning. Assessment was made at 2-weekly intervals at the same time of the day (6–8 hr after the last tablet). Blood pressures were measured blindly in a specially designed out-patient blood pressure clinic, by one observer, using the London School of Hygiene and Tropical Medicine sphygmomanometer. Diastolic pressure was read at Phase V. During the run-in period each patient walked on a treadmill at an incline of 20° for 5 min. The speed was set to produce a plateau tachycardia of greater than 130 beats per min (3–5 kph). This fixed exercise was repeated at each visit.

Throughout the trial, side effects were sought using a questionnaire which was completed at each visit by the patients. Each patient was also asked to estimate well-being by marking a linear scale (graded from 100% very well, no complaints, to 0% very ill).

Statistical analyses were performed using the paired Student's t test for comparison of paired data and calculating correlation coefficients.

Mean blood pressure was taken as

$$\frac{SBP + (DBP \times 2)}{3}$$

Results

Blood pressure
Table 1 shows lying and standing pressures in all 10 patients during the run-in and placebo periods, including the double-blind period when 0 mg of atenolol was given. Average BP was 163/105 mmHg supine and 163/111 mmHg standing with very small standard errors (2 patients showed no change
in BP nor exercise heart rates at any time, and with any treatment, and were considered to be non-compliant: these results are therefore excluded from analysis of dose response). Table 2 shows the mean pressure in 8 patients at each dose level in the supine position and Table 3 the pressures after standing. Pressure falls with each dose are virtually identical.

Resting and exercising heart rate

Table 4 shows average resting and treadmill exercise heart rates for the 8 compliant patients. Resting heart rate fell from 89 to 71 with 25 mg (P<0.001) and there was a further fall to 64 (P<0.02) at 75 mg. Plateau exercising rates fell from 139 to 110 with 25 mg and to 100 with 50 mg. No further fall occurred as the dose was increased to 75 mg and 100 mg.

Compliance

The 2 patients who showed no fall in BP or heart rate in any treatment period were recalled for further study. When challenged by the accusation that no trial tablets had been taken, one admitted to omitting some doses, the other insisted that all the tablets had been swallowed. Each then took a 100 mg tablet at 9.00 a.m. and attended again at 3.00 p.m. for exercise. Then in both there was the expected suppression of heart rate (Table 5).

Side effects

The development of cold hands and feet and tiredness were the only major complaints during the trial. Cold hands and feet with skin colour change to white or blue were noted by 3 patients. This side-effect was related to atenolol but was not dose related - appearing at 25 mg and subsequent doses in 2 patients and 50 mg in a third. Lethargy was a complaint of 5 patients at some time but was as often found during placebo periods as atenolol treatment periods.

The well-being linear scale was marked between 40% (poorly) and 100% (very well, no complaints). The score on all doses of atenolol was identical to that obtained in the randomized placebo and single-blind placebo periods.

Discussion

Dose response for blood pressure

Previous studies have emphasized how flat is the dose response curve for the hypotensive effect of...
Dose response with atenolol

Table 4. Heart rate. Mean heart rate for the 8 patients whose results were analysed

<table>
<thead>
<tr>
<th>Dose of atenolol</th>
<th>Treadmill walking (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 mg</td>
<td>0 0.5 1 1.5 2 2.5 3 3.5 4</td>
</tr>
<tr>
<td>25 mg</td>
<td>71 86 96 102 105 107 109 110</td>
</tr>
<tr>
<td>50 mg</td>
<td>67 79 91 93 96 103 100 100 100</td>
</tr>
<tr>
<td>75 mg</td>
<td>64 82 90 94 97 99 100 100 101</td>
</tr>
<tr>
<td>100 mg</td>
<td>64 83 88 91 98 99 100 101 102</td>
</tr>
</tbody>
</table>

Significance 0 v. 25 mg. P<0.01 at all times 25 v. 50 mg 0 n.s. 0.5 min n.s. 1.0 n.s. 1.5 n.s. 2.0 P<0.05 2.5 n.s. 3.0 P<0.05 3.5 P<0.05 4.0 P<0.05

Table 5. Response of heart rate to varying dosages of atenolol in 2 patients

<table>
<thead>
<tr>
<th>Dose of atenolol prescribed (mg)</th>
<th>Resting heart rate</th>
<th>Plateau exercise heart rate</th>
<th>Resting heart rate</th>
<th>Plateau exercise heart rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (run-in)</td>
<td>108</td>
<td>151</td>
<td>96</td>
<td>160</td>
</tr>
<tr>
<td>0 (run-in)</td>
<td>78</td>
<td>144</td>
<td>78</td>
<td>175</td>
</tr>
<tr>
<td>0 (random)</td>
<td>96</td>
<td>143</td>
<td>84</td>
<td>174</td>
</tr>
<tr>
<td>0 (random)</td>
<td>108</td>
<td>145</td>
<td>84</td>
<td>145</td>
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<td>25</td>
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<td>96</td>
<td>164</td>
</tr>
<tr>
<td>100</td>
<td>96</td>
<td>140</td>
<td>108</td>
<td>165</td>
</tr>
</tbody>
</table>

Results following 100 mg seen to be taken 65 98 82 132

Atenolol in the dose range 50–600 mg daily (Marshall et al., 1977; Petrie et al., 1977; Dollery, 1977). The authors have previously shown that 100 mg of atenolol is as effective as 400 mg daily in maintaining reduction of blood pressure. In this double-blind study the hypotensive effect of 25 mg daily was not significantly different from 100 mg and it must therefore be assumed that the dose response curve lies between 0 and 25 mg daily. It is concluded that clinicians can be advised to use a fixed dose of atenolol of 100 mg daily. It seems most unlikely that higher doses will ever be advantageous.

Dose response for suppression of exercise tachycardia

Suppression of exercise tachycardia appears to be the most suitable method to assess the degree of β-blockade. Shanks et al. (1977) compared doses of 12.5, 25, 50, 100, 200 and 400 mg daily in 5 normal subjects and found a 14% reduction with 12.5 mg, 22% with 25 mg, 25% with 100 mg, and 40% with 400 mg daily. The difference between 25 and 100 mg daily was not significant and the results of the present authors' rather larger study in hypertensives is similar. They chose to measure suppression of exercise heart rate and thereby they estimate the degree of β-blockade 6–8 hr after the last dose of atenolol because the plasma half-life of this β-blocker is about 7 hr. A daily dose of 25 mg produced a 20% fall in exercise tachycardia and 50, 75 and 100 mg daily a 28% fall. The increase in β-blockade between 25 and 50 mg was not paralleled by a further fall in blood pressure. The authors' hope that this study would give further evidence of the association between degree of β-blockade and fall in BP has not been fully realized. The suggestion here that partial β-blockade produces a full hypotensive effect needs confirmation. It appears to be the case that very large doses of atenolol produce a further
fall in exercising heart rate but those who have measured the fall in BP find no difference between 50 and 400 mg daily.

Compliance
The 2 patients considered non-compliant attended each clinic without default and each performed 16 treadmill exercise tests. In none of the 32 exercise tests was there any suppression of tachycardia. By contrast, of the 64 treadmill tests performed in the other 8 subjects on active treatment, only one failed to show the expected suppression of tachycardia. When the drug was seen to be swallowed, both resting and exercise heart rate were suppressed in these 2 patients. The conclusion appears inescapable that, in spite of impeccable handling by the investigator and full compliance in attendance and exercise, neither patient took the tablets.

This experience should warn clinical trialists that even the most careful drug trial may be vitiated by non-compliers. Some objective marker that the tablets have been taken appears essential. Attention has recently been drawn to the high rate of non-compliance in a well conducted BP clinic, Marshall and Barritt (1977). One advantage of the use of β-blocking agents without intrinsic sympathomimetic activity is that the absence of bradycardia suggests non-compliance.

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References
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