Clinical Evaluation of Atenolol in Hypertensive Patients

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SUMMARY Atenolol, a cardioselective β-adrenergic blocking agent, was given as the sole hypotensive drug for 8–12 weeks to 20 patients with hypertension of varying degrees of severity. Initial systolic blood pressure ranged from 162–238 mm Hg (mean ± SEM 196 ± 5.5 mm Hg) and diastolic blood pressure ranged from 105–143 mm Hg (118 ± 2.5 mm Hg). Three patients had accelerated hypertension, six had cardiomegaly with recent exertional dyspnea and three were diabetics. Atenolol, 100–300 mg once daily, controlled both the supine and standing blood pressure and markedly attenuated the initial hypertensive response to severe exercise. In 17 patients (85%), atenolol therapy reduced blood pressure more than 20/10 mm Hg; however, adequate blood pressure control was not achieved in severe hypertension. A significant hypotensive action developed within 2 weeks of treatment, and control of hypertension was maintained for 2 weeks after sudden interruption of therapy. No patient had postural or postexercise hypotension. The drug appeared to exert its maximum hypotensive effect at the 100-mg dosage. The magnitude of the hypotensive response was related to the initial systolic blood pressure (r = 0.77, p < 0.01) and the degree of inhibition of exercise tachycardia (r = 0.66, p < 0.01). The atenolol plasma level and its hypotensive action were not related. Except for impairment of glucose tolerance in diabetic patients, atenolol had minimal side effects.

THE EFFICACY of β-adrenergic blocking drugs for the treatment of hypertension has been well established, but most such drugs lack cardioselectivity and their use has been generally restricted to patients without associated respiratory or peripheral vascular diseases. Atenolol (Tenormin) is a new cardio-selective β-adrenergic blocking agent that has no intrinsic sympathomimetic properties and, unlike propranolol, has no membrane-stabilizing action. Preliminary reports indicate that atenolol may exert a marked antihypertensive action in man. However, previous trials with atenolol were limited to mild or moderate uncomplicated forms of hypertension. The present study was designed to assess the efficacy and safety of this new cardioselective drug in the treatment of varying degrees of hypertension, particularly severe, complicated forms and those associated with cardiomegaly. Some of the factors that might influence the magnitude of the hypotensive action were examined.

Methods

Patients

Twenty male patients who were attending the Cairo Transport Organization Hospital Hypertension Clinic were studied. Patients with a diastolic blood pressure of at least 105 mm Hg were entered into the trial. Clinical evaluation and routine investigations were performed as previously described. These included hematologic, chest x-ray examination, electrocardiography, fundus examination, serum creatinine and creatinine clearance, blood sugar, urinary catecholamines and vanillyl mandelic acid estimations and i.v. pyelography, if necessary.

All patients were employed as bus drivers or conductors at the Cairo Transport Organization. They were 30–64 years old (mean age 49.9 ± 1.64 years [± SEM]). Their body surface area ranged from 1.60–2.12 m² (mean 1.93 ± 0.03 m²). Three patients had recently discovered hypertension, while the others had known hypertension ranging from 1–15 years (mean 5.41 ± 0.95 years). Optic fundi (Keith-Wagner-Barker classification) were normal in only two patients; nine patients had grade I, six patients had grade II, and three had grade III hypertensive retinopathy (hemorrhages and exudates — accelerated hypertension). Six patients had radiologic evidence of cardiac enlargement (cardiothoracic ratio greater than 0.5). Seven patients had electrocardiographic evidence of left ventricular hypertrophy (criteria of Sokolow and Lyon and McPhie). Eleven patients had other electrocardiographic abnormalities in the form of ST-segment, T-wave changes and intraventricular conduction defects. Six patients had a history of classic angina of effort documented by electrocardiographic evidence of myocardial ischemia. Three patients had diabetes mellitus (one patient was insulin-dependent), and one patient had chest wheezes and asthmatic bronchitis. Six patients had a recent history of exertional dyspnea and radiologic evidence of cardiomegaly.

Serum creatinine ranged from 1.1–1.6 mg% (mean 1.3 mg%). All but four patients were receiving various antihypertensive medications when admitted to the trial. Except for nine patients who were hospitalized and limiting their activities for varying periods because of severe hypertension and/or symptoms of dyspnea and chest pain, the rest of patients were ambulatory and doing their routine work. All patients were advised to avoid excess salt in the diet. Each patient volunteered for the study.
Design of the Study

The duration of the study was 16–20 weeks per patient. The study comprised four phases, and in four patients, an additional fifth phase. The first phase was a 4-week placebo run-in period during which all previous therapy was discontinued. This phase was canceled in patients with accelerated hypertension, and the drug was introduced immediately without an initial placebo period. The second phase was 4 weeks of a single daily morning dose of 100 mg of atenolol; the third phase was either a continuation of the 100-mg dose or doubling it to 200 mg, depending on the patient's blood pressure response at the end of the second phase. Patients with blood pressure greater than 170/100 mm Hg were given the 200-mg dosage in phase 3. In the fourth phase, atenolol was discontinued and replaced by a placebo for the second time for a 4-week period. In four patients with resistant hypertension (blood pressure greater than 180/110 mm Hg), a fifth phase of 300 mg of atenolol in a single daily dose was given for 4 weeks, replacing phase 4, followed by the final 4-week placebo period.

Electrocardiographic studies, examination of optic fundi and serum creatinine measurements were made before and 8 weeks after atenolol treatment.

Patients were asked to take atenolol tablets at 7–7:30 a.m. Ambulant patients were seen every 2 weeks and blood pressure was recorded with a standard cuff sphygmomanometer under standard conditions between 10 and 11:30 a.m. by the same observer. The mean of three blood pressure readings (same arm) after 10 minutes resting supine and 2–3 minutes standing was recorded. The diastolic pressure was recorded at phase 5 Korotkoff sounds. Heart rate was checked at the same time. Then every patient was asked to perform a maximal physical exercise of climbing stairs to the point of maximal tolerance (near exhaustion) or to the development of chest pain in anginal patients. The number of stairs and the time taken by each patient were recorded in each visit. Blood pressure and pulse rate were measured within 1 minute of completion of exercise and also 5 minutes later. Hospitalized patients were seen and had their blood pressures checked every day. However, for the purpose of the study design and to make results comparable with other patients, data of blood pressure readings every 2 weeks only were included in this paper.

Tablet counts and body weight were checked at each visit. Initial weight averaged 76 kg. Questions were directed to specific items such as general well-being, dizziness, headaches, shortness of breath, chest pain, wheezes, palpitations, insomnia, cold extremities, nightmares and depression. Patient compliance was confirmed by tablet counts.

Atenolol plasma level was determined in 18 patients using the gas-liquid chromatography technique by the Imperial Chemical Industries Laboratories. Determinations were made after 2 and 6 weeks of atenolol therapy. Blood pressure was measured at the same time of blood sampling. In 15 patients, blood samples were taken 24 hours after atenolol intake and in three patients, 2 hours after administration of the drug.

Results

Blood Pressure

Atenolol reduced both supine and standing arterial pressures in all patients. Table 1 and figure 1 show the blood pressure readings during the various phases of the trial. A significant reduction in blood pressure was achieved by the end of the second week of therapy. At the end of the eighth week, the decrease in systolic blood pressure ranged from 7–58 mm Hg and in diastolic blood pressure, from 5–38 mm Hg. In 85% of patients atenolol therapy reduced blood pressure greater than 20/10 mm Hg. The magnitude of the hypotensive response was related to the level of initial pressure (fig. 2). There was a positive correlation between the reduction in systolic blood pressure and the initial systolic blood pressure ($r = 0.77, p < 0.01$). This relationship did not hold for diastolic blood pressure.

Sudden interruption of treatment produced a gradual rise in blood pressure (table 1, fig. 1).

In all nine patients with mild-to-moderate hypertension (supine blood pressure less than 200/120 mm Hg, normal or grade 1 retinopathy and absence of cardiac hypertrophy), blood pressure was adequately controlled and it decreased from 175/112 ± 3.7/1.5 mm Hg to 148/93 ± 1.8 mm Hg. On the other hand, seven patients in the whole group (35%) failed to achieve a blood pressure of 150/90 mm Hg. These patients were characterized by an initially high blood pressure (average 220/129 mm Hg), six had electrocardiographic abnormalities, four had cardiomegaly and three had accelerated hypertension. Doubling the atenolol dosage in 12 patients to 200 mg/day did not signifi-
Table 1. Observations During the Various Phases of the Trial (n = 20)

<table>
<thead>
<tr>
<th>Blood pressure (mm Hg)</th>
<th>Admission</th>
<th>Placebo</th>
<th>Atenolol (100-200 mg)</th>
<th>Placebo*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 wks</td>
<td>4 wks</td>
<td>2 wks</td>
<td>6 wks</td>
</tr>
<tr>
<td>Supine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>195 ± 4.9</td>
<td>196 ± 5.7</td>
<td>196 ± 5.5</td>
<td>174 ± 3.9</td>
</tr>
<tr>
<td>Diastolic</td>
<td>118 ± 2.2</td>
<td>117 ± 2.4</td>
<td>118 ± 2.5</td>
<td>108 ± 2.4</td>
</tr>
<tr>
<td>Standing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>197 ± 5.3</td>
<td>198 ± 5.4</td>
<td>197 ± 4.6</td>
<td>175 ± 3.7</td>
</tr>
<tr>
<td>Diastolic</td>
<td>120 ± 2.4</td>
<td>118 ± 2.9</td>
<td>119 ± 2.8</td>
<td>110 ± 2.6</td>
</tr>
<tr>
<td>After 1 min exercise</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>218 ± 4.9</td>
<td>223 ± 4.9</td>
<td>225 ± 5.1</td>
<td>194 ± 4.6</td>
</tr>
<tr>
<td>Diastolic</td>
<td>125 ± 2.3</td>
<td>126 ± 2.3</td>
<td>129 ± 2.7</td>
<td>117 ± 2.4</td>
</tr>
<tr>
<td>Pulse rate (beats/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supine</td>
<td>84 ± 3.2</td>
<td>89 ± 2.9</td>
<td>86 ± 1.9</td>
<td>79 ± 1.9</td>
</tr>
<tr>
<td>Standing</td>
<td>90 ± 3.3</td>
<td>91 ± 3.1</td>
<td>88 ± 2.1</td>
<td>80 ± 2.1</td>
</tr>
</tbody>
</table>

*Sixteen patients participated in the second placebo phase; in the other four patients, atenolol dosage was increased to 300 mg/day (fig. 3).

Heart Rate

Atenolol produced a progressive slowing of the heart rate both in the supine and standing positions (table 1, fig. 4). Changes were significant after 2 weeks of treatment (*p < 0.05). Continuation of therapy produced more slowing of the heart rate; however, the differences between changes at the second and eighth weeks were not significant.

Figure 2. Relationship of the reduction in systolic blood pressure (SBP) after atenolol therapy and the initial level of SBP (r = 0.77, p < 0.01).
Postural tachycardia was attenuated with atenolol; the supine and standing cardiac rates were similar during therapy (fig. 4).

Increasing the atenolol dosage from 100 to 200 mg/day caused a decrease in supine heart rate of 7 beats/min ($p < 0.05$).

**Muscular Exercise**

Except for two patients who developed angina, all patients tolerated the maximal exercise test well. Patients were not acquainted with the procedure during the first trial, so some had difficulty in achieving the desirable maximal effort. Therefore, the blood pressure and heart rate measurements during the first admission exercise were excluded. When patients were on placebo, blood pressure rose from 196/118 ± 5.5/2.5 mm Hg to 225/129 ± 5.1/2.7 mm Hg within 1 minute after maximal exercise. At the end of the eighth week of atenolol therapy, blood pressure increased from 161/99 ± 3.6/2.7 mm Hg to 179/106 ± 4.0/2.1 mm Hg. Figure 5 shows the marked reduction of blood pressure at 1 and 5 minutes after exercise during treatment.

Figure 6 shows the changes in the exercise heart rate produced by atenolol. Before treatment, heart rate increased by 36 beats/min (42%) within 1 minute of maximal exercise. After treatment, the heart rate increased by 19 beats/min (26%). The drug produced a
reduction of 29 beats/min (24%) in the maximal exercise heart rate. The slowing of exercise heart rate (1 minute) by atenolol was related to the degree of reduction in supine systolic blood pressure ($r = 0.66$, $p < 0.01$) (fig. 7).

**Atenolol Plasma Level**

Twenty-eight determinations of atenolol plasma level were made in 18 patients. Blood pressure was measured at time of blood sampling. Twenty-five determinations were made 24 hours after intake of the tablet (table 2). In three patients, determinations were made 2 hours after atenolol intake (100 mg); in these patients plasma levels were 0.20, 0.35 and 0.52 $\mu$g/ml. The limit of detection in these analyses was about 0.01 $\mu$g/ml. There was marked variability in plasma level after atenolol administration (table 2). However, atenolol level and the hypotensive effect were not related. In six determinations, nothing was detected in plasma despite the presence of hypotensive action. The duration of therapy did not influence the plasma level, but an increase in dosage produced higher atenolol concentrations in the blood (table 2).

**Effect on ECG, Fundi and Serum Creatinine**

ST-segment and T-wave abnormalities were normalized in four of 13 patients; however, electrocardiographic left ventricular hypertrophy did not regress after therapy. Abnormalities in optic fundi improved in the majority of patients: grade I reverted to normal in three of eight and grade II regressed to grade I in three of six and to normal in one patient. The three patients with grade III regressed to grade II. Serum creatinine decreased from 1.3 to 1.1 mg/100 ml.

**Side Effects**

All patients completed the trial. None of the side effects was severe enough to warrant interruption of atenolol therapy. Four patients complained of cold extremities. Three patients complained of tiredness and fatigue. These two complaints were present predominantly at the start of the treatment by atenolol; however, they subsided and greatly ameliorated with continuation of therapy, especially in the last 2 weeks. Two patients complained of insomnia, one patient complained of dizziness and one of dyspepsia.

Diabetic patients tolerated atenolol as well as the other patients did. However, the insulin requirements had to be increased in the patient with insulin-dependent diabetes. The three diabetic patients had more impairment in the 3-hour glucose tolerance curve, with more hyperglycemic changes. Bronchospasm and asthmatic bronchitis did not worsen with atenolol therapy. Body weight did not change during treatment.

**Table 2. Atenolol Plasma Level**

<table>
<thead>
<tr>
<th>Atenolol dose (mg/day)</th>
<th>Duration of therapy (weeks)</th>
<th>No. of determinations</th>
<th>Atenolol plasma level ($\mu$g/ml)</th>
<th>Range</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>2</td>
<td>12</td>
<td>ND to 0.29</td>
<td>0.09 ± 0.09</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>6</td>
<td>6</td>
<td>ND to 0.18</td>
<td>0.08 ± 0.07</td>
<td></td>
</tr>
<tr>
<td>200</td>
<td>6</td>
<td>7</td>
<td>ND to 0.50</td>
<td>0.18 ± 0.17</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: ND = nothing detected (limit of detection is about 0.01 $\mu$g/ml).
Discussion

Previous trials with \( \beta \)-adrenergic blocking agents as the sole hypotensive agents were usually limited to selected groups of patients with mild-to-moderate uncomplicated hypertension. The present study was designed to examine the efficacy and safety of atenolol, a cardioselective \( \beta \)-adrenergic blocking drug, in a heterogeneous group of hypertensive patients, including patients with mild, moderate, and severe, accelerated hypertension. The drug was given to complicated cases — patients with cardiomegaly, diabetics and a patient with bronchial asthma. Previous studies have shown atenolol to be effective in treating mild and moderate hypertension.\(^7\,8\,12\) However, its use in severe, complicated cases has not been described. The cardioselectivity of atenolol could be expected to reduce the risk of obstructive respiratory symptoms. Moreover, as vascular \( \beta_2 \) receptors are left unblocked by atenolol, it seems probable that acute rises of blood pressure, e.g., due to stress-induced release of circulating catecholamines, would be less marked than \( \beta_1 \) and \( \beta_2 \)-receptor blocking agents (non-cardioselective).\(^18\) The lack of sympathomimetic effect of atenolol would be expected to be an advantage, at least in the treatment of severe hypertension, as has been claimed for propranolol.\(^18\)

The results of the present study demonstrate that atenolol lowers arterial pressure in all grades of hypertension with minimal side effects. Patients with mild-to-moderate hypertension showed the best therapeutic response; blood pressure was adequately controlled in all nine patients in this group. A significant hypotensive action developed within 2 weeks of therapy, and control of hypertension was maintained for 2 weeks after sudden interruption of treatment. The return of blood pressure to the initial placebo level was gradual and took more than 4 weeks (fig. 1). Atenolol controlled both the supine and the standing blood pressure and markedly attenuated the initial hypertensive response to severe exercise. There was neither postural hypotension nor postexercise hypotension. The present study did provide evidence that atenolol was effective over 24 hours. Blood pressure was measured at time of blood sampling for atenolol plasma level 24 hours after drug intake. These measurements and those taken 3–4 hours after administration of atenolol were the same. The persistence of a hypotensive action for 2 weeks after discontinuation of treatment (table 1, fig. 1) was an additional indication of prolonged effectiveness of atenolol. Previous studies showed that once-daily dosing with atenolol controlled blood pressure for at least 24 hours.\(^8\,13\)

Atenolol was given once daily in a single dose of 100–300 mg. The drug appeared to exert its maximum hypotensive effect at the 100-mg/day dosage. This observation is in agreement with the preliminary findings of Amery et al.\(^1\) and Myers et al.,\(^7\) which also showed a flat dose-response relationship between increasing doses of atenolol and changes in arterial pressure. We found that an increase in atenolol dosage from 100 to 200 mg had no significant additional hypotensive effect; it only produced more slowing of the heart rate. An increase in dosage to 300 mg/day was tried in four resistant cases (blood pressure of 180/110 mm Hg) in an effort to achieve better control of hypertension. This increase in dosage decreased blood pressure by an average of 13/8 mm Hg (range 0–22/0–14 mm Hg) (fig. 3). However, one must consider that the somewhat greater fall in blood pressure on the higher dose of atenolol is probably because the high dose was always given after the lower dose and would possibly benefit from the progressive decrease in blood pressure with time.

The magnitude of the hypotensive response was related to the initial systolic blood pressure (fig. 2). There was a positive correlation between the reduction in systolic blood pressure and the initial systolic blood pressure (\( r = 0.77, p < 0.01 \)). Such a relationship has been described with propranolol.\(^17\) The mechanism of this correlation is not clear from the present study.

Atenolol was given to six patients with cardiomegaly and recent exertional dyspnea. The drug was effective and safe. In five patients, shortness of breath was relieved and exercise tolerance markedly improved. Studies in animals have shown that atenolol has no negative inotropic effect.\(^18\) Hemodynamic studies in man have shown that during supine rest, the stroke volume was higher after therapy than before and that myocardial contractility was not depressed.\(^20\) Control of hypertension would relieve the pressure afterload, and the bradycardia would allow better filling of the heart.

One objective of this study was to examine some of the factors that might influence the magnitude of the hypotensive action of atenolol. Previous studies failed to show a clear relationship between cardiac \( \beta \) blockade and the antihypertensive effect of \( \beta \)-blocking agents.\(^21\,22\) To assess the degree of the blockade of intrinsic \( \beta \)-sympathetic drive, exercise was used because it offers a reproducible physiologic adrenergic stimulation. We found a positive correlation between the slowing of the exercise heart rate by atenolol and the degree of reduction in supine systolic blood pressure (\( r = 0.66, p < 0.01 \)) (fig. 7). This finding suggests that part of the hypotensive action of atenolol was related to cardiac \( \beta \) blockade. However, the atenolol plasma level and its hypotensive effect were not related. The plasma level was not influenced by the duration of therapy, but by the dose given (table 2). Large individual differences in the plasma concentration were found. This was in agreement with the observations on other \( \beta \) blockers.\(^23\,24\)

The antihypertensive effect of atenolol was not influenced by the age of the patient, the duration of hypertension, the initial heart rate or the presence of target organ damage. However, the drug was most effective in patients with mild-to-moderate hypertension.

Thus, atenolol is an effective antihypertensive agent. It can be used in the treatment of hypertension of varying degrees of severity, whether complicated or not, although atenolol therapy did not control blood
pressure in severe hypertension. The only side effect that should be carefully considered is the impairment of glucose tolerance in diabetic patients.

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