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Atenolol: Once-daily Cardioselective Beta Blockade for Angina Pectoris

Graham Jackson, M.B., Janice Schwartz, M.D., Robert E. Kates, Ph.D.,
Mark Winchester, M.D., and Donald C. Harrison, M.D.

SUMMARY The physiology, pharmacokinetics, and efficacy of atenolol, a cardioselective β-adrenergic blocking agent, were evaluated in 10 patients with stable angina pectoris in a single-blind, dose-ranging study. After a 1-month control placebo period, atenolol was administered once daily at dosages of 25, 50, 100, and 200 mg for 2-week periods. All patients had fewer anginal attacks and consumed fewer nitroglycerin tablets than during the placebo period. Twenty-four-hour ambulatory ECG recordings showed a decrease in mean hourly heart rate throughout the dosing period, with preservation of diurnal variation. Maximal symptom-limited treadmill exercise tests performed 3 hours after drug ingestion showed significantly increased exercise time and decreased double products for all doses, but especially with 100-mg and 200-mg doses. Exercise time 24 hours after drug ingestion continued to show a decrease in maximum heart rate and double product, with 100-mg and 200-mg doses again being most effective. Atenolol serum levels correlated with percent reduction in exercise heart rate and increased exercise time. Serum levels rose linearly, with an average elimination half-life of about 10 hours after chronic oral dosing. Thus, atenolol was an effective antianginal agent and suppressed resting and exercise-stressed heart rate for 24 hours after ingestion when given in a 100-mg or 200-mg dose once daily.

THE BENEFICIAL EFFECTS of β-adrenergic blockade in the treatment of angina pectoris are well established.1,2 The most widely used agent is propranolol. Since propranolol was introduced, various β-adrenergic blocking agents with differing properties have been developed in an attempt to avoid the side effects of generalized β blockade. Atenolol, a cardioselective β blocker, is one of these newer agents. Because of initial favorable clinical reports in Europe,3–5 we undertook a dose-ranging and antianginal efficacy study of atenolol in patients with stable, exercise-induced angina.

Materials and Methods

Patients
Ten patients, seven men and three women, with a mean age of 55 years (range 35–67 years) participated in the study. Each patient gave written consent after being informed of the details and objectives of the study, and the protocol was approved by the Stanford Medical Committee on the Use of Human Subjects in Research. All had had clinically stable exercise-induced angina for 3 or more months. No patient had valvular heart disease, cardiac failure, obstructive airways disease, hypertension (resting diastolic pressure > 100 mm Hg), diabetes, or thyroid or renal disease.

Drug Dosage Administration

A single-blind protocol was used because of the risks reported with sudden withdrawal of β blockade.6 All drug preparations (including placebo) were given as two identical tablets once daily at 8 a.m. Nitroglycerin was used for pain, but not for prophylaxis, throughout the trial. Placebo was given for the first 4 weeks of the 12-week protocol, which served as an initial control period. In subsequent 2-week periods, patients received 25 mg, 50 mg, 100 mg and 200 mg of atenolol daily. Drug compliance was checked by tablet count and measurement of serum drug levels.

Antianginal Assessment

The patients kept a daily record of anginal attacks and nitroglycerin consumption. These records were reviewed by the investigators every 2 weeks, and side effects were noted. At each visit, supine and standing heart rates were determined from ECG recordings and blood pressures were measured using a standard sphygmomanometer. Only the data of the last week of each 2-week period were used for comparisons to avoid carry-over effects.7

Exercise Testing

During the second week of each treatment period, exercise testing was performed 3 hours and 24 hours after drug ingestion. No food, caffeine or nitroglycerin was consumed within the 2 hours before testing. With continuous ECG monitoring, patients exercised on a motor-driven treadmill until chest pain occurred (symptom-limited). The exercise test began at a constant grade of 10% and 1 mph, with 0.5-mph increments introduced every 3 minutes; a 12-lead ECG was recorded before testing and at 3-minute intervals, and three-lead ECGs were recorded each minute between the 3-minute recordings. The blood pressure was

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recorded at rest and after 1 and 3 minutes of each treadmill stage. Changes in ST segments were measured during and after peak exercise. A downgradually sloping depression of at least 1 mm persisting for 0.08 second or longer in at least five consecutive beats was considered indicative of ischemia. Monitoring was continued for a minimum of 6 minutes after exercise or until values returned to control levels. All anginal episodes stopped after cessation of exercise.

Ambulatory Monitoring

During the second week of each 2-week period, a 24-hour ambulatory recording was performed. This monitoring period included both peak and trough treadmill tests. Patients were encouraged to engage in their normal daily activity and wore recorders on the same day of the week for each test. Avionics recording systems were used and the tapes were analyzed on the Stanford computer system.9 Heart-rate trends were examined throughout the 24-hour period.

Serum Drug Levels

Five ml of heparinized blood was drawn 3 hours (peak) and 24 hours (trough) after atenolol ingestion (concomitant with treadmill testing and ambulatory ECG monitoring). Serum atenolol concentrations were determined by a high-pressure liquid chromatographic method.8

Statistical Analysis

Data were analyzed for statistical significance by the repeated-measures analysis of variance. For variables where statistically significant (at the 5% level) dose-response relationships were detected, further comparison of mean responses at different dose levels was done using a matched-pairs t test.

Anginal Attack Rate and Nitroglycerin Consumption

The mean weekly incidence of angina and nitroglycerin consumption are shown in table 1 and figure 1. Compared with placebo, atenolol reduced the anginal attack rate during all periods of its administration (p < 0.001). A dose response was present with a decreasing number of attacks with increasing dosage. Atenolol at doses of 100 mg and 200 mg was significantly superior to the 25-mg dose (p < 0.001), but there was no significant difference between the 50-mg and 100-mg doses or the 100-mg and 200-mg doses. The 200-mg dose was more effective than the 50-mg dose (p < 0.005). Nitroglycerin consumption declined in a parallel, dose-related fashion. Compared with placebo, all dosages decreased nitroglycerin consumption significantly (p < 0.001), with no significant difference between the 50-mg dose vs 100-mg and 200-mg doses or the 100-mg dose vs the 200-mg dose (table 1 and fig. 1).

Exercise Data

During the initial placebo period, peak and trough tests were not significantly different, verifying the reproducibility of the responses with the protocol (table 2). All atenolol doses significantly reduced resting and exercise heart rate at 3 hours (p < 0.001) and 24 hours (p < 0.001) after ingestion (table 3 and fig. 2). Atenolol was statistically most effective at 100-

<table>
<thead>
<tr>
<th>Table 1. Subjective Data</th>
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<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>Weekly angina attacks</td>
</tr>
<tr>
<td>Weekly nitroglycerin</td>
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<td></td>
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<tr>
<td>Values are mean ± SEM.</td>
</tr>
</tbody>
</table>
mg and 200-mg doses, with no significant difference between the two. The maximal exercise double product (heart rate times systolic blood pressure) at the occurrence of chest pain was significantly reduced at peak and trough testing by all atenolol doses \((p < 0.001)\), but the 100-mg and 200-mg doses were significantly more effective than the 25-mg or 50-mg doses \((p < 0.001)\) (fig. 3). The amount of exercise necessary to produce angina 3 hours after drug ingestion was increased by all atenolol doses. At 24-hours after drug ingestion, however, only 50-mg \((p < 0.01)\), 100-mg \((p < 0.005)\) and 200-mg doses of atenolol \((p < 0.001)\) showed significant improvement compared with placebo (fig. 3). ST depression was significantly reduced 3 hours after drug ingestion by 25-mg and 50-

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**Table 2. Placebo Data**

<table>
<thead>
<tr>
<th></th>
<th>Peak</th>
<th>Trough</th>
<th>(p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting heart rate (beats/min)</td>
<td>72.2 ± 2.3</td>
<td>78.7 ± 3.4</td>
<td>NS</td>
</tr>
<tr>
<td>Exercise heart rate (beats/min)</td>
<td>118.7 ± 4.7</td>
<td>114.6 ± 4.2</td>
<td>NS</td>
</tr>
<tr>
<td>Resting SBP (mm Hg)</td>
<td>141.1 ± 8.8</td>
<td>139.2 ± 7.2</td>
<td>NS</td>
</tr>
<tr>
<td>Resting DBP (mm Hg)</td>
<td>86.7 ± 5.9</td>
<td>86.4 ± 3.8</td>
<td>NS</td>
</tr>
<tr>
<td>Exercise SBP (mm Hg)</td>
<td>167.0 ± 8.8</td>
<td>163.9 ± 7.7</td>
<td>NS</td>
</tr>
<tr>
<td>Exercise time (sec)</td>
<td>413.5 ± 34.9</td>
<td>384.5 ± 30.3</td>
<td>NS</td>
</tr>
<tr>
<td>Exercise ST depression (mm)</td>
<td>1.6 ± 0.3</td>
<td>1.7 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Double product</td>
<td>198.3 ± 16.4</td>
<td>187.8 ± 14.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
Abbreviations: SBP = systolic blood pressure; DBP = diastolic blood pressure; double product = exercise heart rate times systolic blood pressure divided by 100.

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**Table 3. Atenolol Exercise Data**

<table>
<thead>
<tr>
<th></th>
<th>25 mg Peak</th>
<th>25 mg Trough</th>
<th>50 mg Peak</th>
<th>50 mg Trough</th>
<th>100 mg Peak</th>
<th>100 mg Trough</th>
<th>200 mg Peak</th>
<th>200 mg Trough</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting heart rate (beats/min)</td>
<td>62.1 ± 2.1</td>
<td>70.9 ± 2.7</td>
<td>58.5 ± 1.5</td>
<td>67.1 ± 3.0</td>
<td>54.3 ± 1.5</td>
<td>61.5 ± 2.9</td>
<td>60.7 ± 2.9</td>
<td>60.8 ± 2.9</td>
</tr>
<tr>
<td>Exercise heart rate (beats/min)</td>
<td>100.1 ± 3.6</td>
<td>104.4 ± 4.1</td>
<td>96.7 ± 3.1</td>
<td>101.7 ± 4.1</td>
<td>89.5 ± 2.1</td>
<td>99.4 ± 3.9</td>
<td>88.1 ± 2.5</td>
<td>96.9 ± 4.0</td>
</tr>
<tr>
<td>Resting SBP (mm Hg)</td>
<td>131.7 ± 6.0</td>
<td>139.1 ± 7.5</td>
<td>127.1 ± 6.4</td>
<td>132.4 ± 7.0</td>
<td>128.0 ± 7.3</td>
<td>130.8 ± 5.5</td>
<td>127.1 ± 8.0</td>
<td>127.4 ± 7.5</td>
</tr>
<tr>
<td>Resting DBP (mm Hg)</td>
<td>77.9 ± 3.7</td>
<td>81.6 ± 5.5</td>
<td>76.5 ± 2.5</td>
<td>77.9 ± 5.5</td>
<td>75.2 ± 3.3</td>
<td>76.4 ± 4.1</td>
<td>74.4 ± 3.9</td>
<td>70.3 ± 3.5</td>
</tr>
<tr>
<td>Exercise SBP (mm Hg)</td>
<td>149.5 ± 7.5</td>
<td>161.0 ± 7.7</td>
<td>150.1 ± 7.2</td>
<td>154.0 ± 9.1</td>
<td>143.9 ± 6.1</td>
<td>153.1 ± 9.0</td>
<td>145.1 ± 6.9</td>
<td>155.0 ± 8.3</td>
</tr>
<tr>
<td>Exercise time (sec)</td>
<td>477.2 ± 44.9</td>
<td>407.5 ± 34.2</td>
<td>552.0 ± 39.3</td>
<td>447.9 ± 35.7</td>
<td>527.5 ± 39.7</td>
<td>459.0 ± 37.4</td>
<td>541.7 ± 35.3</td>
<td>508.3 ± 38.5</td>
</tr>
<tr>
<td>Exercise ST depression (mm)</td>
<td>1.2 ± 0.3</td>
<td>1.4 ± 0.3</td>
<td>1.06 ± 0.3</td>
<td>1.5 ± 0.2</td>
<td>0.8 ± 0.3</td>
<td>0.9 ± 0.2</td>
<td>0.7 ± 0.4</td>
<td>1.2 ± 0.4</td>
</tr>
<tr>
<td>Double product</td>
<td>151.0 ± 11.9</td>
<td>170.0 ± 13.8</td>
<td>147.0 ± 10.2</td>
<td>159.0 ± 14.9</td>
<td>129.0 ± 8.0</td>
<td>153.0 ± 13.4</td>
<td>128.0 ± 8.7</td>
<td>152.0 ± 14.1</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
Abbreviations: SBP = systolic blood pressure; DBP = diastolic blood pressure; double product = exercise heart rate times systolic blood pressure divided by 100.
curred at the time of treadmill exercise testing. The mean minimum heart rate for the placebo period was 55 beats/min, and occurred during sleep. During administration of 25, 50, 100 and 200 mg of atenolol, the mean minimum heart rates were 52, 52, 47 and 47 beats/min, respectively. Diurnal variation in heart rate was observed. Even with the higher atenolol doses, no heart rates less than 45 beats/min were recorded during the 24-hour period. Figure 5 is a typical R-R interval plot that shows the increase in R-R interval with increasing drug dosage and the narrowing of the range of intervals recorded during atenolol therapy.

Drug Levels

The mean peak steady-state serum atenolol concentrations were 117.4, 257.2, 437.2 and 916.5 ng/ml after 2-week administration of atenolol at doses of 25, 50, 100 and 200 mg, respectively (fig. 6). The peak serum levels increased linearly with increased dosage, suggesting linear bioavailability and pharmacokinetics. The peak concentration during the 200-mg dosing protocol was as high as 2000 ng/ml in one patient. There was significant intersubject variability in peak serum concentrations, with an average coefficient of variation for all four doses of 55%.

The mean trough steady-state serum atenolol concentrations were 23.0, 51.9, 67.8 and 103.7 ng/ml after the 2-week administration of atenolol at doses of 25, 50, 100 and 200 mg, respectively (fig. 6). The trough concentrations were 20.7 ± 10.6% (mean ± SD) of the peak level when all data pairs were considered. Though adequate blood samples were not obtained to permit calculation of disposition parameters, these data suggest an average elimination half-life for atenolol of about 10 hours.

Side Effects and Toxicity Studies

One patient developed mild congestive cardiac failure on 200 mg atenolol (with a peak serum drug concentration of 1000 ng/ml), but this resolved with dosage reduction and diuretic therapy. There were no changes in SGOT, Alk Phos, total bilirubin, FBS, uric acid, BUN, total protein, cholesterol, calcium, inorganic phosphate, albumin, LDH, hemoglobin, hematocrit or white blood count. Nine of the 10 patients have continued on long-term atenolol therapy with no complaints of vivid dreams, hallucinations, depression or insomnia.

Table 4. Heart Rates Derived From 24-hour Ambulatory ECG Recordings

<table>
<thead>
<tr>
<th></th>
<th>Minimum (beats/min)</th>
<th>Maximum (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>55.1 ± 1.0</td>
<td>118.7 ± 4.1</td>
</tr>
<tr>
<td>Atenolol (25 mg)</td>
<td>52.2 ± 1.5</td>
<td>103.5 ± 4.2</td>
</tr>
<tr>
<td>Atenolol (50 mg)</td>
<td>50.3 ± 1.4</td>
<td>94.3 ± 2.0</td>
</tr>
<tr>
<td>Atenolol (100 mg)</td>
<td>47.0 ± 0.8</td>
<td>88.8 ± 4.1</td>
</tr>
<tr>
<td>Atenolol (200 mg)</td>
<td>47.3 ± 1.7</td>
<td>87.7 ± 4.4</td>
</tr>
</tbody>
</table>

Values are mean ± SEM.
timal dosages, atenolol was effective once daily. Another antianginal study reported that atenolol was more effective than practolol. Neither sedative effects nor decreased reaction times after atenolol administration have been reported. Although vivid dreams have been sporadically reported during atenolol therapy, they occur much less frequently than with propranolol. In a report of patients who had nightmares, hallucinations and insomnia on β blockers, almost all noted a reversal of these side effects after changing to atenolol.

The protocol was designed to establish the presence or absence of adequate β blockade throughout the 24-hour period after the oral administration of atenolol once daily. Reduction of peak exercise heart rate was evaluated through treadmill stress testing 3 and 24 hours after atenolol ingestion at the time of peak and trough serum atenolol levels. Twenty-four-hour ambulatory electrocardiographic recordings monitored the heart rates under resting conditions and normal daily activity to exclude major swings in heart rate control. To assess the antianginal efficacy of atenolol, we measured anginal attack rate, consumption of nitroglycerin and changes in exercise tolerance in each patient. By correlating serum atenolol levels with anginal relief and exercise tolerance, we hoped to define the optimum therapeutic dosing range, dosage interval and the therapeutic antianginal serum concentration range.

Our results show that in stable angina, atenolol significantly reduces the frequency of anginal attacks.

**FIGURE 5.** By plotting R-R interval against percent frequency of occurrence, the 24-hour heart rate control is illustrated. With increasing dosage, the plot moves to the right, indicating improved 24-hour heart rate control.

**Discussion**

Beta-adrenergic antagonists are well established in the treatment of angina pectoris. The major beneficial effect is achieved through reduction of myocardial oxygen consumption, primarily by decreasing exercise heart rate and blood pressure. As the mechanism of action of these drugs is competitive inhibition of β receptors, little difference in antianginal benefit of equipotent doses of individual agents would be expected once the maximum reduction of peak exercise heart rate is achieved.

Propranolol, one of the most widely used of the β blockers, has several clinical disadvantages: first, a relatively short pharmacokinetic half-life (4–6 hours), which has prompted (perhaps unnecessarily) frequent dosing intervals; second, nonspecific β blockade with potential pulmonary and peripheral vascular effects; and third, central nervous system side effects (which now constitute a compelling reason for discontinuing β-blocker therapy).

Atenolol, like propranolol, has a pure β antagonist action but lacks intrinsic sympathomimetic activity and membrane-stabilizing activity. Potential advantages of atenolol include its cardioselective β blockade, a plasma half-life of 6–10 hours and a pharmacodynamic half-life of 18 hours, and the lack of significant penetration into the central nervous system (personal communication: Imperial Chemical Corporation Laboratory). A single oral dose of atenolol in normal volunteers has produced blockade of exercise-induced tachycardia for at least 24 hours after ingestion. At least one preliminary antianginal study has shown that atenolol given twice daily is as effective as propranolol and that for op-

**FIGURE 6.** Peak (filled circles) and trough (open circles) steady-state serum atenolol concentration as a function of dose. Each point represents the mean ± SEM of the subjects.
and nitroglycerin consumption, with 100-mg and 200-mg doses being the most effective. The results from 24-hour ambulatory electrocardiographic monitoring showed good control of heart rate throughout the 24-hour dosing period with preservation of the normal nighttime bradycardia. Atenolol significantly prolonged the duration of exercise at the time of peak serum levels and significantly reduced the peak exercise heart rate, double product and ST depression. Though all dose increments significantly reduced exercise heart rate at trough serum levels, only the 50-mg, 100-mg and 200-mg doses significantly increased exercise time when compared with placebo.

In these studies, the serum concentration of atenolol related to the magnitude of the effect and can be used as a dosing guideline. We found a mean trough serum concentration of about 70 ng/ml was necessary to insure adequate therapeutic benefit throughout the 24-hour dosing interval. This level was achieved with a chronic oral dose of 100 mg once daily.

Our studies show that atenolol is a potent antianginal agent. We observed that adequate 24-hour heart rate control is possible with 50-mg, 100-mg or 200-mg doses administered once daily. When only the hemodynamic variables are considered, there is no significant difference between the 50-mg, 100-mg and 200-mg dosages. Regarding anginal relief, the 200-mg dosage was superior to the 50-mg dosage (p < 0.005), but did not significantly differ from the 100-mg dosage, although four patients subjectively benefited most from the 200-mg dosage. This report supports the initial choice of 100 mg of atenolol for antianginal benefit and increase in exercise tolerance when given once daily. If this dose is well tolerated, advancement to 200-mg/day for optimal therapeutic effect may be required, depending on the clinical response. Cardioselectivity is relative and does not imply complete cardiospecificity; therefore, caution is advised with the administration of any β blocker to patients with bronchospastic disorders. In addition, the atenolol dosage or the dosage interval may need to be altered in the presence of renal impairment because excretion is almost entirely via the kidneys. Nonetheless, with its reduced side effects, cardioselectivity and once-daily dosing schedule, atenolol shows promise of significant advantages over currently available β blockers.

Acknowledgments

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