Efficacy and safety of medium- and high-dose diltiazem alone and in combination with digoxin for control of heart rate at rest and during exercise in patients with chronic atrial fibrillation

ARIE ROTH, M.D., EARL HARRISON, M.D., GLADYS MITANI, PHARM. D., JORDAN COHEN, PH.D., SHAHBUDIN H. RAHIMTOOLA, M.B., F.R.C.P., AND URI ELKAYAM, M.D.

ABSTRACT We evaluated the efficacy and the safety of medium- (240 mg/day) and high-dose (360 mg/day) diltiazem alone and in combination with digoxin when used for control of heart rate in 12 patients with chronic atrial fibrillation. Medium-dose diltiazem was comparable to therapeutic dose of digoxin at rest (88 ± 19 vs 86 ± 12 beats/min) but superior during peak exercise (154 ± 23 vs 170 ± 20 beats/min; p < .05). High-dose diltiazem resulted in better control of heart rate than digoxin both at rest (79 ± 17 beats/min; p < .05) and exercise (136 ± 25 beats/min; p < .05) but was associated with side effects in 75% of the patients. Combined therapy of digoxin and diltiazem enhanced the effect of digoxin alone and resulted in significantly better control of heart rate at rest (67 ± 16 beats/min with medium-dose and 65 ± 15 beats/min with high-dose diltiazem) and during peak exercise (132 ± 32 and 121 ± 24 beats/min, respectively). However, the difference in heart rate between these two doses was not significant. Reduction of heart rate combined with concomitant effect on blood pressure resulted in a significant fall in pressure-rate product at rest from 10,077 ± 1708 mm Hg/min on digoxin alone to 7877 ± 1818 mm Hg/min after the addition of medium-dose diltiazem (p < .05) and during exercise from 25,670 ± 3606 to 18,439 ± 4115 mm Hg/min (p < .05). Continued therapy with digoxin combined with diltiazem 240 mg/day for 21 ± 8 days in nine patients showed persistent effect on heart rate and blood pressure without any toxic manifestations or change in serum digoxin (1.5 ± 0.4 vs 1.3 ± 0.4 ng/ml) or plasma diltiazem concentrations (204 ± 72 vs 232 ± 129 ng/ml). In conclusion, medium-dose diltiazem when combined with digoxin is an effective and safe regimen for the treatment of patients with chronic atrial fibrillation and enhances digoxin-mediated control of heart rate both at rest and during exercise.


DIGITALIS has been used traditionally as a drug of choice for control of ventricular rate in patients with atrial fibrillation.1,2 Although the drug is valuable at rest, it is less effective in the control of heart rate response to exercise or other stress-related situations.3,4 Recent studies have demonstrated that the direct effect of verapamil on slowing atrioventricular nodal conduction results in a better control of exercise heart rate in patients with atrial fibrillation.3,5,6 The use of verapamil, however, may be limited in patients with heart disease because of (1) its negative inotropic effect7 and (2) its interaction with digoxin, which leads to a decrease in digoxin renal clearance and therefore, at times, to a marked elevation of serum digoxin concentration and digoxin toxicity.8,9 Diltiazem, another calcium entry–blocking agent, has similar electrophysiologic properties to that of verapamil resulting in a depression of conduction and prolongation of refractory time in the atrioventricular node.10,11 and has shown a beneficial effect on resting heart rate in patients with atrial fibrillation.12 In contrast to verapamil, most of the available data demonstrate no significant interaction between diltiazem and digoxin.13,14 In addition, preliminary data have demonstrated a favorable hemodynamic effect of diltiazem in patients with heart failure.15 Diltiazem therefore

From the Section of Cardiology, Department of Medicine, LAC/USC Medical Center, University of Southern California School of Medicine, and the Clinical Pharmacokinetic Laboratory, University of Southern California School of Pharmacy, Los Angeles.

Supported in part by a grant from the General Clinical Research Center (N 8RR-43), National Institutes of Health.

Address for correspondence: Uri Elkayam, M.D., Director, Inpatient Cardiology, USC School of Medicine, 2025 Zonal Ave., Los Angeles, CA 90033.

Received July 10, 1985; revision accepted Oct. 31, 1985.

316
seems potentially a very attractive agent for the treatment of patients with atrial fibrillation. In this study we evaluated the efficacy and safety of medium (240 mg/day) and large (360 mg/day) doses of diltiazem alone and in combination with therapeutic doses of digoxin in the control of resting and exercise heart rate in patients with chronic atrial fibrillation.

Materials and methods

Patient characteristics. Twelve patients (three men and nine women) between the ages of 34 and 57 years (mean ± SD 48 ± 7) with chronic atrial fibrillation were included in the study group. Patients who had a myocardial infarction in the preceding 3 months or who had angina pectoris, severe heart failure, hypertension uncontrolled by diuretics alone, significant renal or hepatic dysfunction, known conduction system disease, or Wolff-Parkinson-White syndrome were excluded. The etiology of atrial fibrillation was rheumatic mitral valve disease in 11 patients and was unknown in one (table 1). Six patients had previous mitral valve replacement and one had an aortic valve replacement with open commissurotomy of the mitral valve. One of the patients (No. 11) had a history of myocardial infarction that was believed to be secondary to thromboembolic phenomenon rather than atherosclerotic coronary artery disease. None of the patients had clinical evidence for ischemic heart disease. All patients were treated with digoxin, the dose of which was not changed for at least 2 weeks before the initiation of the study. Eight patients received 0.250 mg/day and four patients received 0.375 mg/day. All patients but one (No. 3) received medications other than digoxin during the study. These medications are listed in table 1 and were continued in the prestudy dose throughout the study period. All patients gave informed consent for the study.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yr)/sex</th>
<th>Cardiac disease</th>
<th>Concomitant disease</th>
<th>Digoxin dose (mg/day)</th>
<th>Other medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>57/F</td>
<td>RHD, S/P MV av replacement</td>
<td>DM</td>
<td>0.375</td>
<td>F, KCL, In</td>
</tr>
<tr>
<td>2</td>
<td>53/F</td>
<td>RHD, mitral regurgitation</td>
<td>—</td>
<td>0.375</td>
<td>F, KCL</td>
</tr>
<tr>
<td>3</td>
<td>51/F</td>
<td>—</td>
<td>—</td>
<td>0.250</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>38/F</td>
<td>RHD, S/P MV replacement</td>
<td>—</td>
<td>0.250</td>
<td>C</td>
</tr>
<tr>
<td>5</td>
<td>56/F</td>
<td>RHD, S/P AV replacement and mitral commissurotomy</td>
<td>—</td>
<td>0.250</td>
<td>F, FS, KCL</td>
</tr>
<tr>
<td>6</td>
<td>50/M</td>
<td>RHD, S/P, MV replacement</td>
<td>—</td>
<td>0.375</td>
<td>F, KCL</td>
</tr>
<tr>
<td>7</td>
<td>45/M</td>
<td>RHD, S/P, MV replacement</td>
<td>—</td>
<td>0.25</td>
<td>F, KCL</td>
</tr>
<tr>
<td>8</td>
<td>46/F</td>
<td>RHD, mitral stenosis and regurgitation, tricuspid stenosis</td>
<td>—</td>
<td>0.250</td>
<td>F, P, FS</td>
</tr>
<tr>
<td>9</td>
<td>44/M</td>
<td>RHD, mitral stenosis and regurgitation, aortic regurgitation</td>
<td>—</td>
<td>0.250</td>
<td>F, KCL</td>
</tr>
<tr>
<td>10</td>
<td>47/F</td>
<td>RHD, S/P MV replacement</td>
<td>DM</td>
<td>0.375</td>
<td>KCL, In</td>
</tr>
<tr>
<td>11</td>
<td>34/F</td>
<td>RHD, S/P MV replacement and myocardial infarction</td>
<td>—</td>
<td>0.250</td>
<td>P, HCT, A</td>
</tr>
<tr>
<td>12</td>
<td>56/F</td>
<td>RHD, S/P MV replacement</td>
<td>—</td>
<td>0.250</td>
<td>HCT, KCL A, C, T</td>
</tr>
</tbody>
</table>

A = aldosterone; AV = aortic valve; C = coumadin; DM = diabetes mellitus; F = furosemide; FS = ferrous sulfate; HCT = hydrochlorothiazide; In = insulin; KCL = potassium chloride; MV = mitral valve; P = penicillin; RHD = rheumatic heart disease; S/P = state post; T = Tylenol.
resting upright studies were started within 1 min of assuming the erect position. Diltiazem 240 mg (60 mg qid) was started at 6 P.M. after measurement of baseline supine heart rate and blood pressure. The administration of the first dose of diltiazem was followed by measurement of supine heart rate and blood pressure every 30 min for 2 hr and then at 4 and 6 hr. In addition, heart rate was measured during sleep 10 hr after initiation of diltiazem therapy. Resting and exercise studies were repeated in each patient on the second day of the study according to a schedule as determined on day 1. The dose was then increased to 360 mg/day (90 mg qid), with the first dose being given at 6 P.M. Resting and exercise studies were repeated on day 3 in each patient to assess the effects of high-dose diltiazem combined with digoxin.

Part II: Diltiazem therapy alone. After the completion of part I, digoxin therapy was discontinued and patients were discharged on diltiazem 360 mg/day. Patients were contacted every 2 to 3 days by telephone to ensure compliance to therapy and to inquire about adverse experiences. Seven to 10 days later patients returned for repeated resting and exercise evaluations. After the evaluation, at 6 P.M., diltiazem dose was reduced to 240 mg/day and studies were repeated on the next day in each patient.

Part III: Long-term phase. After the completion of part II, patients resumed their regular digoxin therapy and were treated in addition with diltiazem 240 mg/day to evaluate the long-term effects of this drug combination. Fifteen to 40 days (21 ± 8) later evaluation was repeated in nine of the patients.

Exercise testing. In 10 patients a symptom-limited treadmill exercise test was performed according to standard Bruce protocol and a modified exercise protocol was used in the other two patients. In these patients the treadmill gradient was kept at 0 degrees for one, and at 5 degrees for the other patient while maintaining the standard speed. Blood pressure (standard cuff method) and a 12-lead electrocardiogram were recorded at rest in both the supine and the standing position and then at each minute of exercise. During exercise, electrocardiographic recording was started 20 sec before each minute and was continued for 40 sec or longer. The reported heart rate per minute was based on the number of ventricular beats counted over 40 sec. Rate-pressure product (mm Hg/min) was derived from heart rate times systolic blood pressure. Both resting and exercise tests were performed 5 to 7 hr after the last digoxin dose and 2 to 3 hr after the last diltiazem dose. Duration of exercise was determined for each patient during the initial part of the study on diltiazem therapy alone and was kept constant in all phases of the study.

Drug concentrations. Serum digoxin concentration was determined before each treadmill exercise test and at the same time of the day in every patient. Digoxin serum concentration was measured after the appropriate dilution by a radioimmunoassay technique with a digoxin (125I) radioimmunoassay kit (Abbott Laboratories).

Plasma diltiazem level was examined concomitantly to serum digoxin concentration starting on the second day of the study. Plasma diltiazem concentration was measured by high-pressure liquid chromatography. Bound analysis. Heart rate, blood pressure, and pressure-rate product were compared for both diltiazem doses alone and in combination with digoxin at rest (supine and upright), 1 min of exercise, 50% of exercise time (submaximal exercise), maximal exercise, and 2 min after termination of exercise. The results were analyzed by an analysis of variance for repeated measurements and the Neuman-Keuls multiple range test. The same analysis was used to compare serum digoxin concentrations and plasma diltiazem levels. A Student t test was used to assess effects of long-term therapy with digoxin and medium-dose diltiazem in nine of the patients. A p value <.05 was considered statistically significant. All values were expressed as mean ± SD.

Results

Response of resting heart rate and blood pressure to initiation of diltiazem therapy (figure 2). Resting supine heart rate was 88 ± 9 beats/min before the first dose (60 mg) of diltiazem and did not change significantly 30 and 60 min after its administration (87 ± 16 and 92 ± 19 beats/min, respectively). Significant reduction in heart rate was seen at 90 min (80 ± 11 beats/min; p < .05 vs control) with further decrease at 6 hr (70 ± 11 beats/min; p < .05 vs both control and 90 min). Heart rate measured 24 hr after initiation of therapy and 6 hr after the fourth consecutive diltiazem dose of 60 mg was still significantly lower than the baseline value (65 ± 10 beats/min) and comparable to values measured at 6 hr. Further reduction in heart rate to 60 ± 10 beats/min was seen 10 hr after initiation of therapy at a time when the patients were sleeping. Increasing the dose to 90 mg four times daily did not lead to a significantly greater decrease in heart rate compared with that found during therapy with medium-dose diltiazem (69 ± 13 at 30 min, 66 ± 12 at 60 min, 68 ± 9 at 90 min, 65 ± 12 at 2 hr, and 62 ± 10 beats/min at 6 hr). A significant fall in heart rate was again seen during sleep to 58 ± 10 beats/min. Baseline blood pressure was 119 ± 13/74 ± 11 mm Hg and showed only small and statistically insignificant reduction after the initiation of both medium- and high-dose diltiazem.

Comparative effect of various drug regimens studied

Heart rate (figure 3). Resting. Resting heart rate in the supine position decreased significantly after the addition of medium-dose (240 mg/day) and high-dose diltiazem (360 mg/day) to digoxin. However the difference between the two doses of diltiazem combined with digoxin was not statistically significant. Supine heart rate on either
the medium or high dose of diltiazem alone did not differ significantly from heart rate recorded on digoxin alone.

Both doses of diltiazem had a significant effect on standing heart rate when combined with digoxin. Heart rate recorded on medium-dose diltiazem alone was not significantly different from that seen on digoxin, while high-dose diltiazem alone resulted in a larger reduction in heart rate than digoxin. A comparison between heart rate values on the various drug regimens studied showed that heart rate recorded on the combination of digoxin and diltiazem 360 mg/day was statistically comparable to that seen on digoxin and diltiazem 240 mg/day but lower than heart rate on any other regimen.

**One minute of exercise.** Over 66% of total increase in heart rate during exercise was seen already at the first minute of exercise when digoxin therapy was used alone. The addition of diltiazem or the use of diltiazem alone resulted in a significant reduction in heart rate at the first minute of exercise. The reduction seen with medium-dose diltiazem alone was significantly smaller than that seen with either high-dose diltiazem alone or both diltiazem doses in combination with digoxin. The difference between the effect of medium and high-dose diltiazem dose when added to digoxin was not significant.

**Submaximal exercise.** Heart rate during submaximal exercise on combined therapy was significantly lower than that on digoxin alone or on medium-dose diltiazem alone and was comparable to that measured on high-dose diltiazem alone. The difference between heart rate values on digoxin combined with the two diltiazem doses was not statistically significant.

**Maximal exercise.** Heart rate during maximal exercise was 170 ± 20 beats/min on digoxin alone and fell markedly with combined therapy or diltiazem alone. High-dose diltiazem alone showed a superior effect on exercise heart rate than either digoxin alone or medium-dose diltiazem alone but was found more effective when used in combination with digoxin. No significant difference was found in the heart rate recorded or digoxin combined with either the medium or high dose of diltiazem.

**Recovery from exercise.** Two minutes after exercise heart rate was 116 ± 22 beats/min on digoxin and was decreased to a similar extent with the addition of diltiazem 240 and 360 mg/day. Heart rate on medium-dose diltiazem alone was comparable to that seen on digoxin alone and significantly higher than that recorded on the combined therapy. The use of high-dose diltiazem alone resulted in a significantly lower heart rate than that seen on digoxin alone but higher than the heart rate...
TABLE 2

Systolic and diastolic blood pressure as measured at rest, exercise, and after exercise on the various drug regimens studied

<table>
<thead>
<tr>
<th></th>
<th>Systolic blood pressure (mm Hg)</th>
<th>Diastolic blood pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dig</td>
<td>Dig + DT 240</td>
</tr>
<tr>
<td>Resting supine</td>
<td>118±14</td>
<td>115±12</td>
</tr>
<tr>
<td>Resting upright</td>
<td>118±14</td>
<td>116±13</td>
</tr>
<tr>
<td>1 min exercise</td>
<td>130±11</td>
<td>122±14</td>
</tr>
<tr>
<td>Submaximal exercise</td>
<td>145±16</td>
<td>136±17</td>
</tr>
<tr>
<td>Maximal exercise</td>
<td>151±13</td>
<td>141±18</td>
</tr>
<tr>
<td>2 min after exercise</td>
<td>137±15</td>
<td>124±10A</td>
</tr>
</tbody>
</table>

Dig = digoxin; DT = diltiazem. *p < .05 vs Dig.

recorded when the same dose diltiazem was used in combination with digoxin.

**Blood pressure.** Blood pressure values on all various drug regimens studied are shown in table 2. The effect of diltiazem on systolic and diastolic blood pressure in patients at rest, in the supine position, and during maximal exercise is graphically depicted in figure 4. Diltiazem in both doses either alone or added to digoxin resulted in a significant fall in exercise diastolic blood pressure. A similar effect on systolic blood pressure was seen only with diltiazem alone but not with combined therapy. The use of diltiazem did not lead to any significant change in blood pressure at rest.

**Pressure-rate product (table 3).** The changes in heart rate and systolic blood pressure resulted in a significant reduction in pressure-rate product. This variable (mm Hg/min) fell significantly at rest in the supine position from 10,077 ± 1708 on digoxin to 7877 ± 1818 on digoxin combined with medium-dose diltiazem and to 7703 ± 2150 on digoxin combined with high-dose diltiazem (both p < .05 vs digoxin) (figure 5). A similar effect was seen in the upright position (11,860 ± 2331 on digoxin alone, 9190 ± 2464 on digoxin + diltiazem 240 mg/day, and 8244 ± 2150 on digoxin + diltiazem 360 mg/day; p < .05). The difference between the effect of medium- and high-dose diltiazem when combined with digoxin was not statistically significant. In addition, high-dose diltiazem alone resulted in a significant fall in pressure-rate product when compared with digoxin alone (10,059 ± 2275 vs 11,860 ± 2331; p < .05), which was comparable to that measured on the combined digoxin–diltiazem therapy.

During submaximal as well as maximal exercise and the recovery period, pressure-rate product was significantly reduced with either combined therapy or diltiazem therapy alone as compared with digoxin alone. The effect of medium-dose diltiazem alone, however, was smaller than the effect of combined therapy or high-dose diltiazem alone, whereas the difference in effect between the two doses of diltiazem when combined with digoxin was not significant.

**Long-term therapy.** Nine of the patients were placed on a combination therapy of digoxin and medium-dose diltiazem for 21 ± 8 days (15 to 40 days). At the end of this period heart rate (beats/min) was 76 ± 17 in the supine position (figure 6), 86 ± 18 in the upright position, 112 ± 26 and 132 ± 28 during submaximal and maximal exercise, respectively, and 97 ± 18 at 2 min of recovery from exercise. All these values were significantly lower than those recorded on digoxin therapy alone and comparable to the values recorded after initiation of therapy with digoxin and medium-dose diltiazem. Similarly, the attenuation of diastolic
### TABLE 3

Pressure-rate product (mm Hg/min) at rest, exercise, and after exercise on the various drug regimens studied

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dig</th>
<th>Dig + DT 240</th>
<th>Dig + DT 360</th>
<th>DT 240</th>
<th>DT 360</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting supine</td>
<td>10,077 ± 1708</td>
<td>7877 ± 1818&lt;sup&gt;A,B,C&lt;/sup&gt;</td>
<td>7703 ± 2150&lt;sup&gt;A,B,C&lt;/sup&gt;</td>
<td>10,329 ± 2507</td>
<td>9408 ± 2411</td>
</tr>
<tr>
<td>Resting upright</td>
<td>11,860 ± 2331</td>
<td>9190 ± 2464&lt;sup&gt;A&lt;/sup&gt;</td>
<td>8244 ± 2041&lt;sup&gt;A,B,C&lt;/sup&gt;</td>
<td>12,433 ± 2942&lt;sup&gt;*&lt;/sup&gt;</td>
<td>10,059 ± 2275&lt;sup&gt;A,B&lt;/sup&gt;</td>
</tr>
<tr>
<td>1 min exercise</td>
<td>18,452 ± 2309</td>
<td>12,402 ± 3089&lt;sup&gt;A,B&lt;/sup&gt;</td>
<td>12,240 ± 3744&lt;sup&gt;A,B&lt;/sup&gt;</td>
<td>15,980 ± 3892&lt;sup&gt;*&lt;/sup&gt;</td>
<td>13,944 ± 3758&lt;sup&gt;A,B&lt;/sup&gt;</td>
</tr>
<tr>
<td>Submaximal exercise</td>
<td>22,079 ± 2100</td>
<td>15,652 ± 3354&lt;sup&gt;A,B&lt;/sup&gt;</td>
<td>14,464 ± 2932&lt;sup&gt;A,B&lt;/sup&gt;</td>
<td>18,687 ± 3776&lt;sup&gt;*&lt;/sup&gt;</td>
<td>15,072 ± 2628&lt;sup&gt;A,B&lt;/sup&gt;</td>
</tr>
<tr>
<td>Maximal exercise</td>
<td>25,670 ± 3606</td>
<td>18,439 ± 4113&lt;sup&gt;A,B&lt;/sup&gt;</td>
<td>17,649 ± 2918&lt;sup&gt;A,B&lt;/sup&gt;</td>
<td>21,033 ± 2913&lt;sup&gt;*&lt;/sup&gt;</td>
<td>18,036 ± 3081&lt;sup&gt;A,B&lt;/sup&gt;</td>
</tr>
<tr>
<td>2 min after exercise</td>
<td>15,694 ± 2639</td>
<td>11,208 ± 2523&lt;sup&gt;A,B&lt;/sup&gt;</td>
<td>11,369 ± 2119&lt;sup&gt;A&lt;/sup&gt;</td>
<td>14,586 ± 2772</td>
<td>12,510 ± 1842&lt;sup&gt;A,B&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Dig = digoxin; DT = diltiazem.
Statistical comparisons: *p < .05 vs Dig; <sup><sup>A</sup></sup>p < .05 vs DT 240; <sup><sup>B</sup></sup>p < .05 vs DT 360.

---

**FIGURE 5.** Pressure-rate product as measured at rest and during maximal exercise on the various therapeutic regimen studied. DIG = digoxin; DT 240 = diltiazem 240 mg/day; DT 360 = diltiazem 360 mg/day. *p < .05 vs digoxin; <sup><sup>A</sup></sup>p < .05 vs DT 240.

---

### Pressure-rate product

Blood pressure response to exercise seen initially with the addition of diltiazem 240 mg/day to digoxin was preserved during long-term therapy. Blood pressure was 128 ± 17/76 ± 10 mm Hg during submaximal exercise, 136 ± 22/79 ± 13 mm Hg during maximal exercise, and 123 ± 19/69 ± 12 mm Hg during recovery from exercise. Pressure-rate product on long-term therapy was 8789 ± 2034 mm Hg/min in the supine position, 9478 ± 2103 mm Hg/min upright, 14,295 ± 3776 mm Hg/min during submaximal exercise, 17,722 ± 3188 mm Hg/min during maximal exercise, and 11,958 ± 2766 mm Hg/min during recovery from exercise. All these values were comparable to those recorded after initiation of combined therapy of digoxin and diltiazem 240 mg/day.

**Serum digoxin concentration.** Mean maintenance dose of 0.292 ± 0.062 mg of oral digoxin resulted in baseline serum digoxin concentration of 1.4 ± 0.3 ng/ml and increased slightly but not significantly to 1.5 ± 0.4 and to 1.6 ± 0.4 ng/ml 20 to 21 hr after the addition of medium- and high-dose diltiazem, respectively. In the nine patients who received long-term therapy, the baseline digoxin concentration was 1.4 ± 0.3 ng/ml. This value increased to 1.5 ± 0.4 ng/ml 20 to 21 hr after initiation of therapy and was 1.3 ± 0.4 ng/ml at the end of long-term study period. The differences between these measurements were not statistically significant.

**Plasma diltiazem concentration.** Steady state diltiazem concentrations two to three hr after administration of the last diltiazem dose were 206 ± 78 ng/ml on digoxin + diltiazem 240 mg/day and 267 ± 111 ng/ml on therapy with 240 mg/day of diltiazem alone (p < .05). A significant increase in diltiazem concentrations was noted when the dose of diltiazem was increased to 360 mg/day (400 ± 170 ng/ml on digoxin + diltiazem 360 mg/day and 408 ± 195 ng/ml on diltiazem 360 mg/day given alone; p = NS).

Plasma diltiazem concentrations in nine patients...
who received long-term therapy were 204 ± 72 ng/ml during initial therapy and 232 ± 129 ng/ml during long-term therapy (p = NS).

**Blood chemistry.** Hematocrit values were measured in 11 patients and demonstrated a small decrease (≤20%) in 10, leading to a decrease in mean value from 44 ± 4% at baseline to 40 ± 4% at the end of 7 to 10 days of therapy with high-dose diltiazem (p < .05). No change was seen in any other laboratory values. Hematocrit values were available in eight patients who underwent long-term diltiazem therapy with medium-dose diltiazem and digoxin. In these patients hematocrit values fell only slightly and insignificantly from 44 ± 4% at baseline vs 42 ± 3% at the end of long-term treatment.

**Side effects.** Therapy with high-dose diltiazem was associated with the development of side effects in nine of our 12 patients. Five patients developed leg edema (predominantly the left leg) with no signs of heart failure. This finding was accompanied by periorbital edema and abdominal swelling in one of these patients. Periorbital edema without leg edema was seen in one patient, and three patients complained of abdominal discomfort and constipation. All these findings showed significant improvement within 24 to 48 hr of reduction of the diltiazem dose to 240 mg/day. Two patients developed headaches that responded to reduction of dose in only one of them and necessitated discontinuation of therapy in the other patient. One patient with mild heart failure and depression of left ventricular function (ejection fraction 0.29) developed a marked worsening of congestive heart failure a few days after discontinuation of digitalis therapy while receiving diltiazem 360 mg/day. This patient was treated with a short-term regimen of intravenous furosemide and was allowed to complete the study without any further problems.

**Discussion**

The limitation of digoxin in controlling heart rate in patients with atrial fibrillation was recognized more than 50 years ago. Although the mechanism of action of digitalis on atrioventricular nodal conduction is multifactorial, a stimulation of parasympathetic activity plays a predominant role. Increase in sympathetic tone during stress usually overrides the vagal effect of digoxin and limits its effect on ventricular rate. Failure of digoxin to reduce heart rate during exercise or other stressful situations in patients with atrial fibrillation is of great clinical significance, especially in patients with obstructive mitral valve and ischemic heart disease, and often results in hemodynamic impairment and limitation of exercise capacity.

Our study demonstrates a strong effect of diltiazem on ventricular rate in patients with chronic atrial fibrillation. This agent, by virtue of inhibition of cellular transmembrane calcium influx, exerts a strong electrophysiologic effect that leads to slowing atrioventricular nodal conduction and to prolongation of its functional and effective refractory periods. These effects of diltiazem have been shown to be additive to the depressant action of digoxin on atrioventricular nodal conduction. The addition of a medium dose (240 mg/day) of diltiazem to digoxin resulted in a significant reduction of resting heart rate with attenuation of heart rate response to mild or severe exertion. The effect of diltiazem when combined with digoxin did not correlate with the plasma level of diltiazem (r = .333) and the increase of diltiazem dose to 360 mg/day resulted in only a small and statistically insignificant further reduction in heart rate both at rest and during exercise. In contrast, the effect of diltiazem when used alone was more dose dependent. Medium-dose diltiazem resulted in an effect superior to that of digoxin during exercise but a comparable effect at rest. The use of high-dose diltiazem alone lead to a significantly better heart rate control both at rest and at all levels of activity. Medium-dose diltiazem was more effective when combined with digoxin in the control of both resting and exercise heart rate, despite a significantly lower diltiazem plasma level. The differences in plasma diltiazem concentrations found during therapy with medium-dose diltiazem alone and in combination with digoxin may have been related to the relatively short treatment period with the combined regimen during part I of the study, which may not have allowed a complete steady state.

Although diltiazem has been reported to have a favorable side effect profile, the use of high-dose diltiazem resulted in a high incidence of complications in our study. Seventy-five percent of our patients showed at least one untoward response to the drug. The most common complication was leg edema without evidence of heart failure, which was seen in 41% of the patients. A similar incidence was found by Petru et al. in patients with angina pectoris treated with a similar dose of diltiazem. Predominance of edema in the left leg as seen in our patients has not been described before, and the cause of this finding is unclear. Two patients developed periorbital edema, which was accompanied by leg edema in one of them. To our knowledge periorbital edema has not been previously described in association with the use of diltiazem but has been recently reported in patients receiving nifedipine. Although the development of edema mediated...
by calcium channel–blocking agents has been frequently described,20 its mechanism is not known. The significant fall in hematocrit in our study may suggest that fluid retention and increased blood volume is a potential mechanism. This finding, however, can also be attributed to frequent venipunctures performed at the onset of the study.

Constipation has been reported as a common side effect with the use of verapamil.21 Our study demonstrates that the effect of diltiazem on the gastrointestinal system is dose related and occurs frequently when high doses of this drug are used. Worsening of heart failure in one of our patients when treated with high-dose diltiazem may have been related to the concomitant discontinuation of digoxin therapy. However, since hemodynamic deterioration in patients with heart failure has also been described with other calcium entry–blocking agents in patients with heart failure,7,24 this could also be related to the negative inotropic effect of diltiazem and needs further investigation. It is of importance that side effects were relieved in all but one patient 24 to 48 hr after a reduction of the dose of diltiazem from 360 to 240 mg/day. In one patient headaches persisted in spite of dose reduction and necessitated discontinuation of diltiazem therapy. The strong relationship between diltiazem dose and the incidence of side effects should not be surprising, since it has been shown previously with other calcium entry–blocking drugs.25,26

Recent investigations have shown an important interaction between digoxin and verapamil, another widely used calcium-channel blocker. This drug has been reported to reduce digoxin clearance and to increase serum digoxin concentration and may lead to digoxin toxicity.5,9,27 The present study substantiates previous reports by other investigators18,28 and by us13 demonstrating the lack of drug interaction between digoxin and diltiazem.

In addition to the effect of diltiazem on heart rate, the use of this drug in our patients resulted in a significant attenuation of an increase in blood pressure during exercise. The effect of diltiazem on blood pressure is probably due to its vasodilatory action but may also be related to a fall in cardiac output caused by the negative dromotropic and inotropic effects of the drug.20 The combined change in both heart rate and blood pressure after therapy with diltiazem should result in a reduction in myocardial oxygen demand if contractility is unchanged29 and can benefit patients with ischemic heart disease. However, because the present study was limited almost exclusively to patients with valvular disease, further studies will be needed to assess the potential beneficial effect of diltiazem in patients with atrial fibrillation with other etiologies. Smith et al.31 have recently reported a significantly cumulative effect of diltiazem plasma levels when the drug was given orally every 6 hr for 16 consecutive doses. Although our study demonstrates a significant hemodynamic effect of the drug even 6 hr after its administration, long-term treatment with medium-dose diltiazem did not demonstrate an augmentation of its therapeutic effect or an increase in plasma diltiazem levels.

In summary, this study demonstrates that the addition of diltiazem enhances digoxin-mediated control of ventricular rate at rest and during exercise and concomitantly lowers pressure-rate product and thus can be expected to lower myocardial oxygen consumption. In combination with digoxin, the use of 240 mg/day diltiazem results in a comparable effect to that seen with 360 mg/day but reduces the toxicity associated with high-dose diltiazem. This drug combination can therefore be valuable in the treatment of patients with chronic atrial fibrillation.

We thank Terrance Baruch, M.D., and Lee Freidenberger, R.N., for their assistance in performing the study, the nursing staff of the Clinical Research Center for their excellent care of our patients, Dione Fosdick and Linda Meyer for secretarial assistance, and Joyce Weiss, Ph.D., Stan Azen, Ph.D., and Mary Duda (Clinfo) for their help in the statistical analysis.

References

Vol. 73, No. 2, February 1986
the calcium antagonist diltiazem on atroventricular conduction in chronic atrial fibrillation. Am J Cardiol 55: 98, 1985
Efficacy and safety of medium- and high-dose diltiazem alone and in combination with digoxin for control of heart rate at rest and during exercise in patients with chronic atrial fibrillation.

A Roth, E Harrison, G Mitani, J Cohen, S H Rahimtoola and U Elkayam

Circulation. 1986;73:316-324
doi: 10.1161/01.CIR.73.2.316

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1986 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/73/2/316

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/