Immediate and short-term hemodynamic effects of diltiazem in patients with hypertension

Celso Amodeo, M.D., Isaac Kobrin, M.D., Hector O. Ventura, M.D., Franz H. Messerli, M.D., and Edward D. Frohlich, M.D.

ABSTRACT The immediate effects of intravenous diltiazem effects and short-term (4 weeks) of the oral drug on systemic and regional hemodynamics, cardiac structure, and humor responses were evaluated by previously reported methods in nine patients with mild-to-moderate essential hypertension and in one patient with primary aldosteronism. Diltiazem was first administered in three intravenous doses of 0.06, 0.06, and 0.12 mg/kg, respectively; patients were then treated for 4 weeks with daily doses ranging from 240 to 360 mg (average 300 mg). Intravenous diltiazem immediately reduced mean arterial pressure (from 115 ± 3 to 96 ± 3 mm Hg; p < .01) through a fall in total peripheral resistance index (from 37 ± 3 to 23 ± 2 U/m²; p < .01) that was associated with an increase in heart rate (from 66 ± 2 to 77 ± 3 beats/min; p < .01) and cardiac index (from 3.3 ± 0.3 to 4.3 ± 0.4 liters/min/m²; p < .01). These changes were not associated with changes in plasma levels of catecholamines or aldosterone or in plasma renin activity. After 4 weeks the significant decrease in mean arterial pressure persisted (104 ± 3 mm Hg; p < .01) and there were still no changes in the humoral substances or plasma volume. Renal blood flow index increased (from 368 ± 52 to 462 ± 57 ml/min/m²; p < .01) and renal vascular resistance index decreased (from 0.37 ± 0.06 to 0.26 ± 0.04 U/m²; p < .01), while splanchnic hemodynamics did not change. Left ventricular mass significantly decreased (from 242 ± 16 to 217 ± 14 g; p < .01). Thus, the fall in arterial pressure produced by diltiazem was associated with improved renal hemodynamics and reduced left ventricular mass without expansion of intravascular volume or alterations in circulating humoral substances.


DILTIAZEM is a benzothiazepin derivative calcium antagonist widely used in the management of angina pectoris and currently under investigation for patients with hypertension.1-3 Its antihypertensive effect appears to result from inhibition of calcium entry into vascular smooth muscle, consequently producing arterial dilatation. The precise hemodynamic effects on systemic and regional blood flow are not totally clear. The present study was performed to evaluate the immediate and short-term hemodynamic effects of diltiazem in patients with mild-to-moderate hypertension.

Methods

Ten patients (eight men and two women; seven black and three white) with mild-to-moderate hypertension, including one white man with primary aldosteronism, were the subjects of this report. The remainder, therefore, had essential hypertension.

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Their mean age was 47 ± 11 (range 34 to 69) years. The patients had either never received antihypertensive therapy previously or had all antihypertensive medications discontinued at least 4 weeks before entry into the study.

Clinical evaluation for secondary forms of hypertension had failed to demonstrate a primary cause of hypertension in all patients except the one with primary aldosteronism who received spironolactone throughout the study.

Patients were included in the study only if their diastolic pressures were equal to or higher than 90 mm Hg and less than 120 mm Hg on at least two consecutive outpatient visits during the 2 weeks before diltiazem therapy was instituted.

After at least 2 weeks without antihypertensive therapy the patients were given a placebo for another 2 weeks. Informed written consent, previously approved by our institutional human study committee, was obtained from the patients after they were provided with a detailed description of the protocol.

Hemodynamic assessment. At the end of the second week of the placebo phase, patients were studied in the hemodynamic laboratory after an overnight fast. By a modified Seldinger technique, catheters were inserted into a brachial artery and an antecubital vein and advanced to the shoulder level.4 Continuous recordings of arterial and venous pressures were obtained simultaneously with the electrocardiogram (lead II). Cardiac output was determined at least in duplicate, usually in triplicate, using indocyanine green dye (5 mg each injection). Resting supine hemodynamic measurements were obtained before and after sequential intravenous bolus administration of diltiazem at doses of 0.06, 0.06, and 0.12 mg/kg. In addition, hemodynamic
responses to upright tilt (48 degrees), isometric exercise (hand-grip, 30% of maximum), and Valsalva maneuver were measured before and after the final intravenous dose of diltiazem. The same hemodynamic measurements were obtained after 4 weeks of diltiazem therapy.

M mode echocardiograms were recorded before and after the third intravenous injection of diltiazem as well as after 4 weeks of oral diltiazem therapy. The techniques for left ventricular visualization have been described previously.5 Posterior and septal wall thicknesses and systolic and diastolic dimensions were measured by three independent observers using the same five consecutive cycles. Left ventricular mass was calculated according to the formula of Bennett and Evans.6 Echocardiographic estimates of left ventricular end-systolic and end-diastolic volumes were calculated by the method of Teichholz et al.7

Renal plasma flow and plasma volume were determined by the single injection clearance of 131I-paraminopropionate and RISA,1211 respectively.8 Splanchnic blood flow was obtained from the plasma clearance of injected indocyanine green dye (50 mg).9 Renal and splanchnic vascular resistance were calculated by dividing mean arterial pressure by the respective regional blood flows. Glomerular filtration rate was determined from 24 hr creatinine clearance, and filtration fraction was obtained by dividing glomerular filtration rate by renal blood flow.

Total blood volume and red cell mass were estimated from plasma volume according to the formula9:

\[
TBV = PV/1 - (Hct \times 0.91)
\]

where TBV is total blood volume, PV is plasma volume, Hct is the peripheral hematocrit, and 0.91 is the correction factor for total body hematocrit.

Plasma renin activity and catecholamine levels were determined by the methods of Sealey et al.9 and Peuler and Johnson,10 respectively. Aldosterone was determined by radioimmunoassay technique.11

**TABLE 1**

| Immediate (intravenous drug) and short-term (oral drug) hemodynamic effects of diltiazem |
|---------------------------------------------|-----------------|----------------|----------------|
| Arterial pressure (mm Hg)                  | Short-term oral drug (240–360 mg/day; average 300) |
| Systolic                                    | Control         | 0.06           | 0.06           | 0.12           | 146 ± 4A                      |
| Diastolic                                   | = 141 ± 6A      | = 144 ± 6A     | = 147 ± 6A     | = 146 ± 4A     |
| Mean                                        | = 115 ± 3       | = 104 ± 4A     | = 104 ± 4A     | = 104 ± 3A     |
| Heart rate (bpm)                            | = 66 ± 2        | = 75 ± 4       | = 76 ± 3       | = 77 ± 3       |
| Cardiac index (l/min/m²)                    | = 3.3 ± 0.3     | = 3.9 ± 0.3    | = 4.0 ± 0.3B   | = 4.3 ± 0.4A   |
| Stroke volume index (ml/m²)                 | = 50 ± 5        | = 53 ± 3       | = 54 ± 3       | = 56 ± 4       |
| Total peripheral resistance index (U/m²)    | = 37 ± 3        | = 27 ± 2A      | = 26 ± 2A      | = 23 ± 2A      |
| Ejection time (msec)                        | = 310 ± 6       | = 308 ± 7      | = 307 ± 7      | = 303 ± 7      |
| Mean rate of left ventricular ejection index (ml/sec/m²) | = 163 ± 16 | = 173 ± 12 | = 176 ± 14 | = 187 ± 18 | = 164 ± 12 |
| Left ventricular stroke work index (U/m²)   | = 105 ± 10      | = 98 ± 7       | = 99 ± 7       | = 99 ± 9       |

Results are expressed as mean ± SEM for nine patients with essential hypertension and one patient with primary aldosteronism receiving the intravenous medication and eight with essential hypertension and one with primary aldosteronism receiving short-term treatment. When data were calculated excluding results in the patient with aldosteronism there were no differences by average or statistics.

*Ap < .01; *p < .05 compared with control.

**THERAPY AND PREVENTION—HYPERTENSION**

**Treatment.** After evaluation of the hemodynamic responses to intravenous diltiazem, patients were started on diltiazem therapy for 4 weeks and then evaluated again by the same hemodynamic and biochemical methods. The initial diltiazem dose was 200 mg capsules twice a day. The dosage was increased to three capsules twice a day during the third and fourth weeks if the dosage was considered inadequate to control the patient’s blood pressure. Adequate control of blood pressure was defined as a fall in resting supine diastolic pressure to below 90 mm Hg or a reduction of 10 mm Hg or more for those patients whose pretreatment diastolic pressures were at least 90 but 100 or less mm Hg. The final dose of diltiazem (after 4 weeks) ranged from 240 to 360 mg/day, with an average of 300 mg/day.

**Statistical study.** One-way analysis of variance with repeated measures was used to compare baseline to immediate and short-term effects of diltiazem. Subsequent to significance tests, Dunnett’s test was used to make pairwise comparisons between baseline and treatment values.12
TABLE 2
Responses to hemodynamic maneuvers before (baseline) and after intravenous and short-term oral (4 weeks) therapy with diltiazem

<table>
<thead>
<tr>
<th></th>
<th>Isometric exercise</th>
<th></th>
<th>Upright tilt</th>
<th></th>
<th>Valsalva maneuver</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Intravenous</td>
<td>Short-term oral</td>
<td>Baseline</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>24 ± 5</td>
<td>28 ± 6</td>
<td>28 ± 4</td>
<td>7 ± 1</td>
<td>14 ± 2</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>3.0 ± 6</td>
<td>15 ± 6</td>
<td>10 ± 3</td>
<td>−14 ± 25</td>
<td>−33 ± 4</td>
</tr>
<tr>
<td>Heart rate</td>
<td>18 ± 6</td>
<td>16 ± 4</td>
<td>19 ± 4</td>
<td>10 ± 4</td>
<td>−1.5 ± 3</td>
</tr>
<tr>
<td>Total peripheral resistance</td>
<td>22 ± 6</td>
<td>14 ± 6</td>
<td>17 ± 5</td>
<td>26 ± 3</td>
<td>72 ± 8</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM of percent change from supine resting responses as compared with baseline.

TABLE 3
Hormonal responses to diltiazem

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Intravenous drug</th>
<th>Short-term oral drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norepinephrine (pg/ml)</td>
<td>300 ± 54</td>
<td>293 ± 38</td>
<td>319 ± 39</td>
</tr>
<tr>
<td>Epinephrine (pg/ml)</td>
<td>44 ± 17</td>
<td>39 ± 7</td>
<td>35 ± 7</td>
</tr>
<tr>
<td>Dopamine (pg/ml)</td>
<td>12 ± 1</td>
<td>13 ± 1</td>
<td>17 ± 3</td>
</tr>
<tr>
<td>Aldosterone (ng/dl)</td>
<td>11 ± 3</td>
<td>8 ± 2</td>
<td>8 ± 1</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml/h)</td>
<td>1.6 ± 0.6</td>
<td>0.7 ± 0.2</td>
<td>2.2 ± 0.5</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM. Note that in this table we have excluded the data from one patient with primary aldosteronism from the averages even though his inclusion did not change the statistical results.

with reflex increases in heart rate and cardiac output (p < .01). Ejection time, stroke volume, left ventricular stroke work, and mean rate of left ventricular ejection did not change (table 1). When these data were calculated excluding results from the patient with primary aldosteronism, neither the average or statistics changed significantly. After the intravenous injection of diltiazem the cardiovascular responses to isometric exercise and the Valsalva maneuvers were unmodified. However, a different response of cardiac index to passive upright tilt was observed (−14 ± 2% decrease before intravenous diltiazem vs −33 ± 4% decrease after intravenous diltiazem; p < .01). Moreover, total peripheral resistance response to upright tilt was greater after intravenous diltiazem (26 ± 3% before vs 72 ± 8% after; p < .01) (table 2). The responses of plasma renin activity and aldosterone and catecholamine levels were unchanged by diltiazem (table 3). Similarly, cardiac structure and function did not change (table 4).

Four week treatment. Five patients had their doses of diltiazem increased from 240 to 360 mg/day in order to achieve adequate arterial pressure control; at 4 weeks pressures in all patients were under control. This significant reduction in mean arterial pressure was a continuation (104 ± 3 mm Hg; p < .01) of the effect achieved by intravenous diltiazem, although the reduction in total peripheral resistance index was no longer significant statistically (37 ± 3 vs 33 ± 2 U) and cardiac index and heart rate returned to baseline levels (table 1). It was of interest that those patients with pretreatment plasma renin activity less than 1.2 ng/ml/hr showed persistent reduction in total peripheral resistance, whereas those (three patients) who had pretreatment plasma renin activity of 1.2 ng/ml/hr or more demonstrated a return of total peripheral resistance toward pretreatment levels despite continued control of pressure (table 5). Left ventricular mass measured by M mode echocardiography was reduced

TABLE 4
Cardiac structure and function before and after diltiazem

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Intravenous drug</th>
<th>Short-term oral drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior wall thickness (cm)</td>
<td>1.1 ± 0.05</td>
<td>1.1 ± 0.1</td>
<td>1.1 ± 0.04</td>
</tr>
<tr>
<td>Septal thickness (cm)</td>
<td>1.2 ± 0.07</td>
<td>1.2 ± 0.1</td>
<td>1.2 ± 0.05</td>
</tr>
<tr>
<td>Left ventricular mass (g)</td>
<td>242 ± 16</td>
<td>236 ± 29</td>
<td>217 ± 14</td>
</tr>
<tr>
<td>Left ventricular internal diastolic diameter (cm)</td>
<td>4.7 ± 0.1</td>
<td>4.7 ± 0.1</td>
<td>4.7 ± 0.1</td>
</tr>
<tr>
<td>Left ventricular internal systolic diameter (cm)</td>
<td>3.2 ± 0.2</td>
<td>4.1 ± 0.4</td>
<td>3.1 ± 0.2</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>62 ± 4</td>
<td>62 ± 7</td>
<td>62 ± 4</td>
</tr>
<tr>
<td>Fractional fiber shortening of left ventricle (%)</td>
<td>33 ± 3</td>
<td>34 ± 5</td>
<td>34 ± 4</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM. 

*p < .05 compared with control.
from 242 ± 16 to 217 ± 14 g (p < .05) (table 4).

Renal blood flow increased from 368 ± 52 to 462 ± 57 ml/min/m² (p < .01) as renal vascular resistance index decreased (from 0.37 ± 0.06 to 0.26 ± 0.04 U/m²; p < .01). There was no significant change in glomerular filtration rate but the renal filtration fraction decreased (from 29 ± 4% to 21 ± 3%; p < .01) (table 6). Plasma volume and splanchnic blood flow and resistance did not change (table 6).

As with intravenous diltiazem, 4 weeks of treatment failed to produce any significant change in plasma renin activity or aldosterone or catecholamine levels (table 3).

Discussion

The results of this study demonstrate that after intravenous diltiazem there was an immediate dose-related reduction in mean arterial pressure produced by a fall in total peripheral resistance that was most likely associated with a reflex increase in heart rate and cardiac output, although plasma catecholamine levels did not change. Previous studies have found similar results. 

Safar et al. observed that similar reflexive sympathetic adjustments disappeared 25 min after intravenous diltiazem. They hypothesized that this reflex cardiac stimulation was dampened either by the action of diltiazem on baroreceptor function or by a calcium-dependent release of neurotransmitter from post-ganglionic nerve endings. However, they also noted that the increased heart rate could have resulted from a direct effect on larger arteries. Diltiazem seems to have different effects on small and large arteries, dilating the arterioles and reducing total peripheral resistance, but having no effect on large arteries. We also calculated changes in large arterial distensibility by dividing arterial pulse pressure by stroke volume and confirmed the earlier report demonstrating that diltiazem had no immediate effect on large arterial distensibility. We also extended that observation by demonstrating that the compound also had no effect on distensibility after 4 weeks of therapy (0.71 ± 0.08; 0.54 ± 0.07, and 0.63 ± 0.07, before treatment, after intravenous drug, and after 4 weeks on oral drug, respectively).

The significant immediate reduction in mean arterial pressure observed after intravenous diltiazem persisted throughout the 4 week treatment period, although the significant fall in total peripheral resistance did not continue as heart rate and cardiac index returned to pretreatment levels. Interestingly, those patients who continued to demonstrate a significant fall in total peripheral resistance all had pretreatment plasma renin activity of 1.2 ng/ml/hr or less, and those with greater plasma renin activity failed to demonstrate this response even though their pressures remained controlled.

These results are in agreement with previous reports demonstrating greater effectiveness of calcium entry–blocking drugs in patients with lower plasma renin activity. In this regard it was of interest that the patient with the greatest reduction in arterial pressure in our study had primary aldosteronism; he demonstrated a 20% fall in mean arterial pressure and a 15% reduction in total peripheral resistance. Guthrie et al. and Millar et al. have described impairment of adrenal steroidogenesis after calcium channel–blocker therapy in normal subjects. Such an effect could explain the greater blood pressure reduction in our patient with primary aldosteronism. However, his plasma aldosterone levels increased from 72 to 120 and 104 ng/dl after intravenous drug and 4 weeks of oral therapy, respec-

### TABLE 6

<table>
<thead>
<tr>
<th>Index</th>
<th>Control</th>
<th>After short-term therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total blood volume (ml)</td>
<td>4864 ± 355</td>
<td>5612 ± 295</td>
</tr>
<tr>
<td>Red cell mass (ml)</td>
<td>1823 ± 160</td>
<td>2100 ± 126</td>
</tr>
<tr>
<td>Plasma volume (ml/cm)</td>
<td>18 ± 1</td>
<td>20 ± 1</td>
</tr>
<tr>
<td>Renal blood flow index (ml/min/m²)</td>
<td>368 ± 52</td>
<td>462 ± 57</td>
</tr>
<tr>
<td>Splanchnic blood flow index (ml/min/m²)</td>
<td>362 ± 43</td>
<td>416 ± 46</td>
</tr>
<tr>
<td>Renal vascular resistance index (U/m²)</td>
<td>0.37 ± 0.06</td>
<td>0.26 ± 0.04</td>
</tr>
<tr>
<td>Splanchnic vascular resistance index (U/m²)</td>
<td>0.35 ± 0.04</td>
<td>0.27 ± 0.03</td>
</tr>
<tr>
<td>Filtration fraction (%)</td>
<td>29 ± 4</td>
<td>21 ± 3</td>
</tr>
<tr>
<td>Glomerular filtration rate (ml/min)</td>
<td>122 ± 11</td>
<td>116 ± 11</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM.

^p < .01 compared with control.
tively. Perhaps this lack of reduction in aldosterone levels reflects the fact that our patient did not have normal aldosterone production before treatment due to his adrenal tumor. Alternatively, his persistent elevated level of aldosterone could have resulted from additional spironolactone stimulation.

Despite unchanged cardiac output from pretreatment levels after 4 weeks of therapy, renal blood flow increased and renal vascular resistance decreased, whereas splanchic blood flow and vascular resistance did not change. These findings underscore the difference between diltiazem and other agents with more uniform vascular effects and potential differences among those agents within the calcium antagonist “group.” Nevertheless, this observation confirms earlier studies demonstrating increased renal blood flow after diltiazem in normotensive man and extends the findings to patients with hypertension.

Pseudotolerance due to expanded intravascular volume associated with pressure reduction was not observed with diltiazem since plasma volume remained unchanged after 4 weeks of treatment, confirming previous reports with another calcium antagonist and with diltiazem. This failure to expand plasma volume may be explained, in part, by a natriuretic action of calcium-channel antagonists, but may also have been produced by diltiazem’s renal hemodynamic action. These findings provide further credibility for the use of calcium antagonists as monotherapeutic agents in the treatment of hypertension.

Left ventricular mass decreased after 4 weeks of therapy. In this regard, a previous report from our laboratory and others demonstrated that other calcium-channel blockers reduced left ventricular mass in spontaneously hypertensive rats. This reduction could result from either reduced ventricular afterload, which plays an important part in the development and progression of ventricular hypertrophy, or from reduction in the number of intracellular calcium ions, which are necessary for protein synthesis. Several other agents previously reported to induce regression of ventricular hypertrophy in animals and man and that inhibit adrenergic cardiac input by angiotensin converting–enzyme activity also may reduce calcium entry and perhaps protein synthesis.

In summary, diltiazem appeared to be a useful anti-hypertensive agent in patients with mild-to-moderate hypertension. The agent was well tolerated and, in this study, was without side effects. In addition, left ventricular mass decreased within 1 month and renal blood flow increased. For these reasons, calcium antagonists, and more specifically diltiazem, may be an alternative means of initial therapy. This latter concept is strengthened by the failure of intravascular volume to expand after pressure reduction.

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