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Hormonal and Hemodynamic Effects of Short- and Long-term Clonidine Therapy in Patients with Mild-to-Moderate Hypertension*

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Two studies of the responses to clonidine as the sole antihypertensive drug in the treatment of mild-to-moderate hypertension are reported. In the first, 11 patients with mild hypertension were treated with 0.1 mg clonidine twice daily for eight weeks. Those patients with “low renin” hypertension (n = 7) were noted to show an increase in plasma renin activity; the patients with “normal renin” hypertension (n = 4) tended to show a decrease. Both groups had a similar decrease in blood pressure. The changes in renin activity correlated significantly (p < 0.01) with the small changes in endogenous creatinine clearance (r = 0.84). In the second study, 16 patients with mild-to-moderate essential hypertension were treated for three months with 0.2 mg clonidine three times daily. Blood pressure decreased from 167 ± 4/105 ± 2 to 140 ± 3/90 ± 2 mm Hg (p < 0.01). Blood pressure changes correlated with decreases in plasma catecholamines (r = 0.61, p < 0.001) and heart rate (r = 0.78, p < 0.001). No significant changes in cardiac output, blood volume, renal blood flow, or glomerular filtration rate were noted. Clonidine is an effective and safe therapy when used as the sole medication in treating mild-to-moderate hypertension.

Sympathetic inhibitors such as guanethidine and reserpine have been associated with decreased effectiveness with prolonged use. Fluid retention and blood pressure increases have also been seen with methyldopa, which is thought to lower blood pressure through a central mechanism, but which also has peripheral sympathetic effects. Effectiveness of these drugs is generally restored by adding diuretic therapy. There are little data on the occurrence or frequency

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CHEST / 83 / 2 / February, 1983 / Supplement

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of this phenomenon with clonidine, which decreases sympathetic tone through a central mechanism. The following studies investigated the acute and chronic hormonal and hemodynamic consequences of treatment of mild-to-moderate hypertension with clonidine.

**METHODS**

The first study evaluated the response to 0.1-mg clonidine twice daily in 11 male outpatients with mild hypertension. Plasma renin activity (PRA) was measured after two to three hours of ambulation, baseline without medication for four weeks, and at one, four, and eight weeks during medication. At each clinic visit, the patients brought a 24-hour urine collection for analysis of sodium and creatinine excretion.

The second investigation evaluated 16 patients (15 men and one woman) with mild (diastolic blood pressure 90 to 104 mm Hg) to moderate (diastolic blood pressure 105 to 119 mm Hg) hypertension receiving a fixed dose of clonidine, 0.2 mg three times daily. The patients were hospitalized and given a constant 120-mEq sodium, 100-mEq potassium daily diet for five days preceding the control period (four weeks with no medications) and for the treatment periods (one week and three months). Urine collections were obtained for the 24-hour period preceding the control and the one-week and three-month studies. Basal supine blood pressure and pulse rate determinations were made, and blood was obtained for PRA, plasma aldosterone, and total plasma catecholamines. Glomerular filtration rate (GFR) and effective renal blood flow were determined by the disappearance from the blood of technetium 99m (Tc) ethylene thiamine penta acetic acid and of iohydronate sodium I 131 (I) following a bolus injection. Blood volume was calculated by the distribution of iodinated 131 serum albumin (I). In five patients cardiac output determinations were performed by radiocardiography. Between hospitalizations the patients were followed up as outpatients and ate an unrestricted diet.

In both studies the patients were selected from the Sepulveda Veterans Administration outpatient clinics. Patients' ages ranged from 28 to 65 in the first study and 35 to 64 years in the second. Secondary causes of hypertension and the presence of significant target organ damage were excluded by results of physical examination, chest roentgenogram, ECG, serum creatinine, and rapid sequence intravenous pyelography. All antihypertensive medications were discontinued at least four weeks prior to the start of each study, and the patients were instructed to avoid the use of all other medications throughout the trials. The data are presented as the means ± SEM. Dunnett's method was used when comparing control with subsequent time points. The unpaired t test was used in comparisons of groups. Linear least squares analysis was performed on regression equations.

**RESULTS**

In the first study the PRA at baseline (3.7 ± 1.7 ng/ml/hr) did not change significantly throughout the study, increasing slightly to 4.5 ± 0.8 ng/ml/hr at eight weeks. A divergent pattern was noted when the "low renin" patients (ambulatory PRA<1.0 ng/ml/hr, n = 7) were compared with "normal renin" subjects (n = 4). The low renin subjects showed an increase in PRA from a baseline of 0.7 ± 0.1 to 4.4 ± 1.0 ng/ml/hr (p < 0.05) at eight weeks, while the normal renin patients had a decreasing pattern (from 9.2 ± 3.4 to 4.7 ± 1.7 ng/ml/hr). The difference between these responses was significant (p < 0.05). The blood pressure response was similar in the two groups, with normal renin patients decreasing from a baseline of 168 ± 6/102 ± 4 to 149 ± 7/99 ± 5 mm Hg and low renin patients decreasing from 167 ± 6/104 ± 4 to 152 ± 7/95 ± 2 mm Hg at eight weeks. The changes in PRA correlated negatively with small changes in creatinine clearance (r = −0.84, p < 0.001), although the relationship was not significant within the low and normal renin subgroups. Overall, creatinine clearance was not significantly changed. The low renin and normal renin groups did not differ significantly with regard to age, body weight, urinary sodium excretion, or baseline electrolytes.

The results of the second study are summarized in Table 1. There was a greater blood pressure response to the larger dose of clonidine used in this study, with a decrease from baseline of 167 ± 4/105 ± 2 to 139 ± 3/89 ± 2 mm Hg (p < 0.01) at one week and 140 ± 3/90 ± 2 mm Hg at three months (p < 0.01). Pulse rate decreased from 84 ± 2 to 69 ± 2 (p < 0.01) at three months, and this change correlated with the change in mean arterial pressure (r = −0.78, p < 0.01).

Glomerular filtration rate did not change significantly from a baseline of 105.7 ± 7.5 ml/min. At one week the value was 99.8 ± 7.4 and at three months 104.8 ± 5.8 ml/min. Effective renal blood flow fell slightly from a control value of 711.0 ± 66.8 to 622.0 ± 60.0 at one week and 652.7 ± 43.7 ml/min at three months (NS). In five patients cardiac output remained stable: 5,248 ± 184 ml/min at baseline, 5,160 ± 145 at one week, and 5,180 ± 210 at three months. Calculated peripheral resistance decreased from a control value of

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**Table 1—Responses to Clonidine, 0.2 mg 3 Times Daily (n = 16)**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Baseline</th>
<th>1 Wk</th>
<th>3 Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>167 ± 4</td>
<td>139 ± 3*</td>
<td>140 ± 3*</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>105 ± 2</td>
<td>89 ± 2*</td>
<td>90 ± 2*</td>
</tr>
<tr>
<td>Pulse rate, beats/min</td>
<td>84 ± 2</td>
<td>67 ± 2*</td>
<td>69 ± 2*</td>
</tr>
<tr>
<td>Glomerular filtration rate, ml/min</td>
<td>106 ± 8</td>
<td>100 ± 7</td>
<td>105 ± 6</td>
</tr>
<tr>
<td>Renal blood flow, ml/min</td>
<td>711 ± 67</td>
<td>622 ± 60</td>
<td>653 ± 44</td>
</tr>
<tr>
<td>Plasma renin activity, ng/ml/hr</td>
<td>2.9 ± 1.0</td>
<td>2.7 ± 0.8</td>
<td>1.8 ± 0.3</td>
</tr>
<tr>
<td>Plasma aldosterone, ng/dl</td>
<td>14.2 ± 0.9</td>
<td>13.5 ± 1.2</td>
<td>13.6 ± 1.5</td>
</tr>
<tr>
<td>Plasma catecholamines, pg/ml</td>
<td>183 ± 12</td>
<td>101 ± 8*</td>
<td>124 ± 8*</td>
</tr>
<tr>
<td>Blood volume, ml</td>
<td>4,682 ± 109</td>
<td>4,595 ± 232</td>
<td>4,536 ± 240</td>
</tr>
<tr>
<td>Urinary sodium, mEq/day</td>
<td>89 ± 5</td>
<td>86 ± 4</td>
<td>91 ± 8</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>80.3 ± 3.2</td>
<td>78.5 ± 2.5</td>
<td>81.3 ± 3.2</td>
</tr>
</tbody>
</table>

*p<0.01.
1,852 ± 86 to 1,569 ± 67 at one week and 1,600 ± 72 dynes sec cm⁻² at three months (p<0.01). Blood volume in the entire group did not change significantly (4,662±169 at control, 4,595±232 at one week, and 4,836±240 ml at three months).

The PRA was 2.9±1.0 ng/ml/hr at control and fell to 2.7±0.8 at one week and 1.8±0.3 ng/ml/hr at three months (NS). Plasma aldosterone was 14.2±0.9 ng/dl at baseline, 13.5±1.2 at one week and 13.6±1.5 ng/dl at three months (NS). Plasma catecholamines decreased from 182.7±11.9 pg/ml control levels to 101.2±7.6 at one week and 123.9±8.0 pg/ml at three months (p<0.01). The change in plasma catecholamines correlated with the change in mean blood pressure (r = 0.61, p<0.001).

As in the first study, an inverse relationship between renin activity changes and changes in GFR was noted (change from baseline at three months of basal PRA vs change from baseline at three months GFR, r=-0.69, p<0.001). Side effects of dry mouth and drowsiness were noted in both studies. Five of 11 subjects in the first study and ten of 16 in the second study noted one or both of these symptoms. These effects tended to decrease with time and did not necessitate dose adjustment or discontinuation in any of the patients.

**Discussion**

These studies in a predominantly male population were performed to analyze the consequences of short- and long-term administration of clonidine as the sole antihypertensive agent in mild to moderate essential hypertension. Although others have suggested that the antihypertensive action of clonidine correlates with changes in the renin-angiotensin-aldosterone system, we did not find such a relationship. In fact, we noted a similar antihypertensive response in low renin patients who tended to show an increase in PRA levels with clonidine therapy. These changes in PRA may have physiologic consequences, since the changes in this parameter correlated with the small fluctuations in GFR, supporting a role for the renin-angiotensin system in the autoregulation of glomerular filtration. Overall, however, no significant effect of clonidine therapy was noted with regard to GFR or renal blood flow.

The decrease in plasma catecholamines and the correlation of this parameter with blood pressure response implicates the sympathetic nervous system as the mechanism of clonidine's effectiveness. It should be noted, however, that plasma catecholamines tended to increase between one week and three months of clonidine therapy, whereas the antihypertensive action was persistent. Heart rate was equally decreased at one week and three months and showed an even better correlation with the blood pressure changes. The central action of clonidine, therefore, might involve mechanisms beyond suppression of sympathetic activity.

In our subset of patients in whom cardiac output determinations were done, the data suggest that cardiac output is not impaired and that peripheral resistance is decreased. No evidence of fluid retention was seen in the analysis of body weight or blood volume determinations, although because of the variability of these measurements and the number of subjects studied, we cannot exclude the possibility that some fluid accumulation could occur in some subjects. These studies were performed after stabilizing sodium intake at each study point. It is conceivable that higher sodium intakes could have fostered fluid retention, but blood pressure was well maintained, and weight gain did not occur during the outpatient (uncontrolled sodium intake) portion of the trial.

The sustained antihypertensive action of clonidine over a three-month period without impairment of cardiac or renal function and without fluid retention provides a rationale for the use of this drug as the sole antihypertensive agent in patients with mild-to-moderate hypertension.

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