Clonidine in the Elderly Hypertensive*

Monotherapy and Therapy With a Diuretic

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Forty-eight elderly patients with uncomplicated mild essential hypertension entered two drug regimens. In group 1, clonidine monotherapy (n = 15), clonidine was titrated to achieve goal blood pressure (<90 mm Hg diastolic) in dosages of 0.05 mg twice daily to 0.2 mg three times daily. Blood pressure decreased without major side effects (p<0.001). Three patients required small doses of diuretic after six months of clonidine monotherapy. In group 2, step-care therapy (n = 33), clonidine was added to chlorthalidone, 25 mg daily, for three weeks. Eight patients achieved the goal blood pressure with chlorthalidone, 25 required clonidine (0.1 mg to 0.3 mg twice daily) to achieve blood pressure control. Side effects of clonidine did not require discontinuation of therapy. Retrospective analysis of up to 2½ years of clonidine plus diuretic (n = 51) showed a similar blood pressure reduction. Clonidine can be used effectively with or without a diuretic in the elderly hypertensive.

The results from large-scale trials have demonstrated the benefits of treating mild hypertension. In the Australian study, two thirds of the patients required two or more medications to achieve goal blood pressure. Elderly patients are particularly susceptible to adverse drug reactions because of the physiologic and pathologic changes that occur with increasing age, and the interactions increase with the number of drugs prescribed. Multiple drugs in the treatment of geriatric hypertension can impair compliance. The metabolic effects of diuretic therapy (hypokalemia, hyperglycemia, hyperuricemia, and hyperlipidemia) are increasingly being appreciated as a cause for concern because they may potentiate the risks of cardiovascular disease.

This study was designed to investigate the potential of clonidine, a centrally acting sympathetic inhibitor, as step 1 therapy in the management of hypertension in the elderly. Dosage required to achieve goal blood pressure was carefully titrated. The efficacy of adding clonidine to small doses of diuretic (chlorthalidone, 25 mg daily) was also examined in the patients who did not achieve goal blood pressure with the diuretic alone. Long-term clonidine therapy as a second drug was also examined in a retrospective analysis of the patient population followed in the Hypertension Screening and Treatment Clinic, Sepulveda VA Medical Center.

METHODS

Study Patients

Forty-eight elderly patients (aged 60 to 84 years) with uncomplicated mild essential hypertension were studied. All patients had been without antihypertension medications for four weeks and were placed into two groups. Group 1, clonidine monotherapy, had 15 patients (12 men and three women). The initial dosage of clonidine was 0.05 mg orally twice daily and was titrated weekly until the goal blood pressure was achieved. The titration schedule was as follows: 0.05 mg, 0.1 mg, and 0.2 mg twice daily, and 0.2 mg three times daily. Patients were followed in the hypertension clinic bimonthly for six months after achieving goal blood pressure.

Group 2, step-care therapy, consisted of 33 patients given diuretics as initial therapy, using chlorthalidone, 25 mg daily for three weeks. Patients with diastolic blood pressure levels between 90 and 100 mm Hg at this time were given clonidine treatment, with a titration regimen of 0.1 mg, 0.2 mg, and 0.3 mg, all twice daily. Patients were followed up for four weeks after achieving goal blood pressure, and the final blood pressures were used for the analysis. The clonidine was tapered over two weeks.

Patients were seen in the morning, four hours after taking antihypertension medication. Blood pressure was taken in the sitting position. Routine laboratory and ECGs were taken at the end of the control period, diuretic period, and after clonidine therapy.

In group 3, retrospective analysis, the charts of all 51 geriatric patients in the Hypertension Screening and Treatment Clinic who had ever been given clonidine after a maximum dosage of diuretic (either hydrochlorothiazide, 50 mg twice daily, or metolazone, 5 mg daily) were analyzed.

Student's t paired analysis was used for statistical evaluation. Results were expressed as mean ± SEM. A probability value of p<0.05 was considered significant.

RESULTS

Clonidine Monotherapy

Significant blood pressure reduction was achieved both in the systolic and diastolic blood pressure levels in the 15 patients given clonidine alone (Table 1). The total dose of clonidine per day varied from 0.1 to 0.6 mg, with five patients responding to the lowest dose. Dry mouth, drowsiness, and constipation were the major side effects of clonidine therapy and did not require discontinuation of therapy in the period of follow-up. After six months of clonidine monotherapy, three patients required small doses of diuretic (metolazone 2.5 mg daily)—because of an average weight gain of 2.25 kg in two women, and the need to reduce clonidine dosage in one man patient who complained of drowsiness.

Clonidine With Diuretics

The blood pressure of eight patients was controlled with chlorthalidone at 25 mg/day (Table 1). Twenty-five patients

Table 1—Blood Pressure Response in Clonidine Therapy with and without Diuretic

<table>
<thead>
<tr>
<th>Group</th>
<th>Control</th>
<th>Posttreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine monotherapy (n = 15)</td>
<td>168 ± 5/102 ± 2</td>
<td>132 ± 4/84 ± 3*</td>
</tr>
<tr>
<td>Step-care therapy (n = 8)</td>
<td>172 ± 4/102 ± 2</td>
<td>146 ± 2/85 ± 2*</td>
</tr>
<tr>
<td>Diuretic + clonidine (n = 25)</td>
<td>173 ± 2/104 ± 3</td>
<td>136 ± 2/85 ± 2*</td>
</tr>
<tr>
<td>Retrospective Analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretic + clonidine (n = 51)</td>
<td>186 ± 6/108 ± 5</td>
<td>128 ± 4/82 ± 3*</td>
</tr>
</tbody>
</table>

*p<0.001.
entered clonidine titration therapy; the dosages required to achieve the goal blood pressure ranged from 0.2 to 0.6 mg/day. Thirteen of the 25 patients achieved goal blood pressure with the 0.2-mg daily regimen. Blood pressure was maintained for four weeks without major side effects. Tapered discontinuation of clonidine therapy resulted in a gradual return of blood pressure to pretreatment level. Two patients complained of palpitations in the first 24 hours of complete withdrawal from clonidine.

**Retrospective Analysis of Long-term Clonidine Therapy Added to a Diuretic**

This study analyzed the efficacy of chronic clonidine therapy in diuretic-treated mild-to-moderate geriatric hypertension. The mean age of this group of 51 patients was 65 years (range, 61 to 81 years). Dosages of clonidine varied from 0.2 mg/day to 0.6 mg/day, and duration of follow-up was at least six months and up to 24 years. If the maximum dosage of diuretic did not achieve goal blood pressure, clonidine was added and titrated from 0.2 mg to 0.6 mg/day. Significant reduction of blood pressure was achieved in both systolic and diastolic blood pressure. The most common side effects were dry mouth, drowsiness, and constipation. Six patients were moved into other regimens because of side effects. Two patients complained of drowsiness, two of sexual dysfunction (not clearly related to the drug), and one each of dry mouth and dizziness. In these patients, 22 had serum potassium levels below 3.5 mEq/L, and two had levels below 3.0 mEq/L on at least one occasion despite potassium supplements. Seven patients had fasting blood glucose levels greater than 150 mg/dl, and ten patients had uric acid levels over 10 mg/dl.

**DISCUSSION**

Patients in the clonidine monotherapy group achieved goal blood pressure with relatively small doses of clonidine. Five patients required only 0.05 mg taken twice daily. Despite some symptomatic side effects of dry mouth, drowsiness, and constipation, there were no metabolic or hemodynamic alterations noted with clonidine monotherapy. The anti-hypertensive effect was maintained with long-term clonidine therapy.

Two of the women were given additional diuretic therapy for inappropriate weight gain at six months. This was attributed to fluid retention, although blood pressure remained well controlled, and edema was not evident. One patient received diuretics to reduce the clonidine dosage and the accompanying side effect of drowsiness.

The Australian study has highlighted the difficulty in achieving goal blood pressure with diuretics alone. We were able to achieve goal blood pressure in only 25 percent of our step-care therapy group with diuretics alone. In geriatric hypertension, it was found that a relatively small dose of diuretic minimized the metabolic side effects when compared with the full dose of diuretic in our retrospective analysis.

Diuretic therapy is associated with several metabolic disturbances. Hypokalemia may precipitate arrhythmias, particularly in the patient with myocardial infarction. Hyperglycemia, hyperuricemia, and hyperlipidemia are all risk factors for cardiovascular disease. In this report, we found that many elderly patients respond to low doses of clonidine without diuretic therapy and without development of these metabolic abnormalities. When diuretics are used, the lowest effective dose can minimize the occurrence of these problems, particularly in the geriatric patient whose metabolism of medications may be reduced.

**REFERENCES**

4. Hypertension Detection and Follow-up Program Cooperative Group. Five-year findings of the Hypertension Detection and Follow-up Program: I. Reduction in mortality of persons with high blood pressure, including mild hypertension. JAMA 1979; 242:2562-77

**Central Mechanisms of Clonidine and Propranolol in Man**

**Quantitative Pharmaco-EEG with Antihypertensive Compounds**

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Direct CNS effects of clonidine (0.2 mg) and propranolol (40 mg and 50 mg) were established in healthy young male subjects within three hours after oral administration. They were demonstrated in two studies using procedures of the Quantitative Pharmaco-EEG (QPEEG) method. Quantitatively, the greatest CNS effects were attained with 0.2 mg clonidine followed by 80 mg, and finally by 40 mg propranolol. Based on the computer-analyzed EEG (CEEG) profiles obtained and using the HZI Research Center CEEG data base, the psychotropic properties of these compounds were predicted. Propranolol, in the 40-mg dose, showed a similarity to vigilance-enhancing compounds, whereas the 80-mg dose and the 0.2-mg dose of clonidine were established as primarily similar to mood-elevating (sedative antidepressant) drugs. However, despite some overall similarities in the mode of action between the high dose of propranolol and the clonidine, some differences in their CNS effects were detected based on their secondary effects (anxiolytic and sedative effects, respectively).

In a series of publications, the psychotropic properties of clonidine and propranolol, two potent antihypertensive

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