Value of Chlorthalidone Plus Reserpine in Moderately Severe and Severe Hypertension

A Two-Year Study

By Frank A. Finnerty, Jr., M.D., Nikos Kakaviatos, M.D., and Victor Chupkovich, M.D.

Despite claims to the contrary,1-4 experience in this clinic over the past 6 years has found little difference in the antihypertensive, diuretic, or "potassium-sparing qualities" among the various thiazide diuretics including chlorthalidone. All these agents have also caused hyperglycemia and hyperuricemia. The only difference between chlorthalidone and the thiazide diuretics has been its long duration of action. This long duration of action has made chlorthalidone an excellent agent to combine with reserpine (a drug whose peak action is not witnessed for several weeks). Studies5,6 have demonstrated that the diuresis produced by 100 mg. of chlorthalidone is still in evidence 48 to 72 hours after its administration, permitting a 2 to 3 times a week schedule. Practical experience attests, however, that the patient is more likely to adhere to a treatment schedule when the medication is administered once a day. For this reason 50 mg. of chlorthalidone was combined with 0.25 mg. of reserpine, allowing once a day administration. The present communication analyzes the effect of this combination when administered to 121 patients with moderately severe or severe hypertension over a 2-year period.

Method and Materials

One hundred twenty-one patients with moderately severe or severe hypertension have been followed for an average of 23 ± 3 months. The patients were chosen from the hypertensive clinic of the District of Columbia General Hospital and from the private practice of one of the authors. One hundred nine patients were diagnosed as moderately severe and 12 patients were diagnosed as having severe hypertension. The characteristic findings in both groups of patients are outlined in tables 1 and 2. None of the patients was considered to have mild hypertension.

All the patients had undergone the standard clinic and laboratory studies routinely used to evaluate the hypertensive state, including history and physical examination, urinalysis, electrocardiogram, and chest x-ray. The arterial pressure was determined by the auscultatory method in the sitting and standing positions. The mean arterial pressure was calculated as the arithmetic mean (systolic plus diastolic divided by 2). The average control arterial pressure represents the average of the last six readings of the arterial pressure prior to the beginning of the study. The average arterial pressures during the experimental period represent the average of 24 determinations of arterial pressure in the sitting position.

In addition serum sodium and potassium, 1-hour postprandial blood glucose, and serum uric acid determinations were performed on all patients. The electrolyte determinations were performed photometrically by the method of Berry, Chappell, and Barnes.7 The blood glucose was performed by the method of Nelson and Somogyi,8 and the uric acid by the method of Kern and Stransky.9

The patients were examined at intervals of 2 weeks and the laboratory procedures were repeated at intervals of 3 to 4 months. Sodium was not restricted in the diet except in the 13 patients with congestive heart failure. These 13 patients were the only ones who received supplemental potassium (potassium chloride 1 Gm. four times a day).

Each of the 109 patients with moderately severe hypertension received a tablet* consisting

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*Supplied as Regroton by Geigy Pharmaceuticals, Division of Geigy Chemical Corp., Ardsley, New York.
Table 1

Characteristic Findings in 109 Patients with Moderately Severe Hypertension

<table>
<thead>
<tr>
<th>Sex</th>
<th>Male—56</th>
<th>Female—53</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>Age</td>
<td>46 ± 6.8 years</td>
</tr>
<tr>
<td></td>
<td>Mean arterial pressure</td>
<td>152 ± 16 mm. Hg</td>
</tr>
<tr>
<td></td>
<td>Blood urea nitrogen</td>
<td>24 mg. % (15-35)</td>
</tr>
<tr>
<td>Fundi (Keith-Wagner)</td>
<td>Normal</td>
<td>12 patients</td>
</tr>
<tr>
<td></td>
<td>Grade I</td>
<td>7 patients</td>
</tr>
<tr>
<td></td>
<td>Grade II</td>
<td>90 patients</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>Normal</td>
<td>31 patients</td>
</tr>
<tr>
<td></td>
<td>Left ventricular hypertrophy</td>
<td>66 patients</td>
</tr>
<tr>
<td></td>
<td>Left ventricular hypertrophy and congestive heart failure</td>
<td>13 patients</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>Normal</td>
<td>48 patients</td>
</tr>
<tr>
<td></td>
<td>Left ventricular hypertrophy</td>
<td>51 patients</td>
</tr>
<tr>
<td></td>
<td>Old infarction</td>
<td>6 patients</td>
</tr>
<tr>
<td></td>
<td>Bundle-branch block</td>
<td>4 patients</td>
</tr>
</tbody>
</table>

Table 2

Characteristic Findings in 12 Patients with Severe Hypertension

<table>
<thead>
<tr>
<th>Sex</th>
<th>Male—7</th>
<th>Female—5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>Age</td>
<td>45 ± 9</td>
</tr>
<tr>
<td></td>
<td>Mean arterial pressure</td>
<td>180 ± 14 mm. Hg</td>
</tr>
<tr>
<td></td>
<td>Blood urea nitrogen</td>
<td>31 mg. % (22-55)</td>
</tr>
<tr>
<td>Fundi</td>
<td>Grade III</td>
<td>9 patients</td>
</tr>
<tr>
<td></td>
<td>Grade IV</td>
<td>3 patients</td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>Left ventricular hypertrophy</td>
<td>12 patients</td>
</tr>
<tr>
<td></td>
<td>Left ventricular hypertrophy and congestive heart failure</td>
<td>8 patients</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>Left ventricular hypertrophy</td>
<td>7 patients</td>
</tr>
<tr>
<td></td>
<td>Old infarction</td>
<td>4 patients</td>
</tr>
<tr>
<td></td>
<td>Bundle-branch block</td>
<td>1 patient</td>
</tr>
</tbody>
</table>

of 50 mg. of chlorthalidone plus 0.25 mg. of reserpine once a day and no other antihypertensive or diuretic medication. In 29 patients this combination represented the initial antihypertensive therapy; in 80 patients this combination was substituted for alpha-methyl-dopa (750 mg. to 1,000 mg./day) plus hydrochlorothiazide (50 mg./day) plus reserpine (0.25 mg./day) in 37 patients, hydrochlorothiazide (50 mg./day) plus reserpine (0.25 mg./day) plus aresoline (100 mg./day) in 43 patients. At the end of 12 months it was decided to add 50 mg. of hydralazine (25 mg. administered twice a day) to those patients whose mean arterial pressure had not fallen more than 15 per cent.

In the 12 patients with severe hypertension, hydralazine (100 mg./day in 10 patients) or alpha-methyl-dopa (750 mg. per day in two patients) was added to the chlorthalidone-reserpine combination at the outset.

Results

The average mean arterial pressure in the 109 patients with moderately severe hypertension at the beginning of the study period was 152 ± 17 mm. Hg; the average systolic pressure was 173 ± 27 and the average diastolic pressure was 118 ± 12 mm. Hg (fig. 1). At the end of the first 12 months the average mean arterial pressure had fallen to 129 ± 8 mm. Hg (a 13-per cent reduction); the average systolic pressure was 148 ± 16 and Circulation, Volume XXXII, July 1965
CHLORTHALIDONE PLUS RESERPINE

The average diastolic pressure was 110 ± 11 mm Hg. Postural hypotension was not observed. At this point this group could be subdivided into 91 patients whose average mean arterial pressure had fallen 20 per cent or more and 18 patients whose mean arterial pressure had not fallen below this figure. In the 91 patients the mean arterial pressure had fallen from an average of 150 ± 15 to 112 ± 9 mm Hg (a 26-per cent average reduction). The systolic had fallen from an average of 175 ± 14 to 130 ± 15 mm Hg and the diastolic had fallen from an average of 125 ± 9 mm Hg to 95 ± 12 mm Hg. In each of these subjects there had been more than a 20-per cent reduction in mean arterial pressure. Despite this fall in arterial pressure the therapeutic response is classified as poor in six of these patients. Severe nasal congestion developed in four, loss of appetite in one, and acute gouty arthritis not controlled by colchicine or probenicid developed in another. At the end of the study period the arterial pressure in these patients remained at approximately the same level. Significant also was the marked improvement in congestive heart failure in eight of the 13 patients.

In the remaining 18 patients with moderately severe hypertension the mean arterial pressure fell from an average of 159 ± 6 to 143 ± 12 mm Hg at the end of the first year (10-per cent reduction); the systolic pressure fell from an average of 185 ± 16 to 160 ± 14 mm Hg and the diastolic pressure fell from an average of 133 ± 13 to 125 ± 12 mm Hg. The addition of hydralazine in a daily dose of 50 mg resulted in a further reduction in arterial pressure from 143 ± 12 to 119 ± 16 mm Hg (a 15-per cent average reduction when compared to the control); the systolic pressure fell from an average of 160 ± 14 to 140 ± 15 mm Hg and the diastolic pressure fell from an average of 125 ± 12 to 100 ± 14 mm Hg. In the 29 patients in whom chlorthalidone plus reserpine represented the initial antihypertensive therapy the mean arterial pressure fell from an average of 148 ± 17 to 115 ± 9 mm Hg (a 23-per cent average reduction); the systolic pressure fell from an average of 180 ± 18 to 140 ± 14 mm Hg whereas the diastolic pressure fell from an average of 118 ± 16 to 90 ± 17 mm Hg. Eighteen of these patients showed an excellent response (more than a 20-per cent fall in mean arterial pressure without toxicity), 10 showed a good response (15- to 20-per cent fall in mean arterial pressure with minimal or no toxicity or drug resistance), and one patient showed a poor response (less than a 10-per cent fall in mean arterial pressure or the presence of severe toxicity with or without a fall in arterial pressure).

In the 43 patients in whom chlorthalidone plus reserpine was substituted for hydralazine plus hydrochlorothiazide plus reserpine the control mean arterial pressure was 152 ± 15 mm Hg, under previous therapy the average mean arterial pressure was 115 ± 20 mm Hg, and under chlorthalidone plus reserpine was 109 ± 15 mm Hg. In the 37 patients in whom chlorthalidone plus reserpine was substituted for alpha-methyl-dopa plus hydrochlorothiazide plus reserpine the control mean arterial pressure was 155 ± 16 mm Hg; under previous therapy the average mean arterial pressure was 122 ± 14 mm Hg and under chlorthalidone plus reserpine was 117 ± 14 mm Hg. When chlorthalidone plus reserpine was substituted for hydralazine plus hydrochlorothiazide plus reserpine, the average mean arterial pressure during chlorthalidone plus

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Figure 1
Changes in arterial pressure in 109 patients with moderately severe hypertension during the 2-year study period.
reserpine was equal to prior therapy in two patients, higher than previous therapy in one, and lower than previous therapy in 34 patients. When chlorthalidone plus reserpine was substituted for alpha-methyl-dopa plus hydrochlorothiazide plus reserpine, the mean arterial pressure during chlorthalidone plus reserpine was equal to prior therapy in two patients and was less than prior therapy in 41 patients.

In summary then at the end of the first year of the study 56 (51 per cent) of the 109 patients with moderately severe hypertension who were treated with a combination of chlorthalidone plus reserpine alone showed an excellent response, 29 (27 per cent) a good response, and 24 (22 per cent) a poor response. The addition of 50 mg. of hydralazine in 18 patients increased the incidence of excellent response at the end of the study to 63 per cent, increased the incidence of good response to 31 per cent, and decreased the incidence of poor response to 6 per cent.

In the 12 patients with severe hypertension the combination of hydralazine plus chlorthalidone plus reserpine or alpha-methyl-dopa plus chlorthalidone plus reserpine resulted in a reduction in mean arterial pressure from an average of 180 ± 14 to 136 ± 20 mm. Hg (a 24-per cent reduction); the systolic pressure fell from an average of 222 ± 25 to an average of 165 ± 28 mm. Hg and the diastolic pressure fell from an average of 140 ± 8 to 108 ± 19 mm. Hg. Eight of these patients demonstrated an excellent response, three good, and one poor. Papilledema disappeared in all three patients 3 months after institution of therapy, retinopathy decreased in six of the nine patients by the end of the first year, and congestive heart failure, present in four patients, cleared in 5 months. One patient died with acute coronary thrombosis.

**Electrolyte Changes and Toxicity**

There were no significant changes in the serum sodium or potassium. A transient increase of 60 to 100 mg. in blood sugar level occurred in seven male and four female patients without a history of prior diabetes. Discontinuation of therapy for a 2-week period allowed the blood sugar level to return to control values in all patients. Four male and eight female patients had known diabetes prior to the study. No significant change in the blood sugar level occurred in these patients during the study.

Hyperuricemia (more than a 4.0-mg. per cent uric acid) developed in 88 of the 123 patients. The normal range of uric acid in our laboratory varies between 2 to 4 mg. per cent. In 54 patients the range of uric acid varied between 4 and 10 mg. per cent, whereas in 34 patients the uric acid was above 10 mg. per cent. Eight male patients without prior symptoms of gout developed gouty arthritis with hyperuricemia. The addition of colchicine and probenecid promptly controlled the gouty state in seven of these patients. Three patients with a history of gout prior to the study had no exacerbation during the 2-year period of the study. Nasal congestion developed in four patients and loss of appetite in one.

**Discussion**

The data presented adequately demonstrate that the combination of chlorthalidone and reserpine represents a simple, effective, and relatively nontoxic method for the treatment of most patients with moderately severe hypertension. Although the treatment of mild hypertension has usually been relatively simple, consisting of a single agent administered two or three times a day, the therapy of moderately severe hypertension by its very nature has been complicated, usually consisting of several agents administered three or four times a day. Thus, until recently most patients with moderately severe hypertension treated in this clinic have received combinations of a thiazide and reserpine plus hydralazine, veratrum, or ganglion-blocking agents, which meant that they were receiving at least 6 to 8 pills a day. The inconvenience to the patient not to mention the frequent mix-up of tablets greatly increased the problem of the physician in regulating the medication and unnecessarily increased the incidence of side effects. One of the obvious advantages of the combination of chlorthalidone plus
CHLORTHALIDONE PLUS RESERPINE

reserpine, therefore, is that it can be administered in a single tablet once a day. The absence of drug resistance or the development of tachyphylaxis during the 2-year duration of this study seems to be another advantage of chlorthalidone plus reserpine. Drug resistance was not noted in a single patient.

The excellent to good responses in so many patients with moderately severe hypertension attest to the efficacy of the combination. Expressed in another way, chlorthalidone plus reserpine resulted in more than a 15-per cent fall in mean arterial pressure without drug toxicity in 85 (78 per cent) of the 109 patients with moderately severe hypertension. It should be emphasized again that none of the patients in this study had only mild hypertension. Objective evidence of vascular disease was present in every patient. The excellent response over a 2-year period included more than simply a reduction in arterial pressure. Not a single patient showed evidence of progression of vascular disease nor did any vascular complication develop. The therapeutic response in only six of these 109 patients (6 per cent) with moderately severe hypertension was classified as poor. This poor therapeutic response was not because of a lack of sufficient reduction in arterial pressure but because of the development of gouty arthritis or nasal congestion.

The synergism of both reserpine and chlorthalidone with hydralazine was demonstrated in the 18 patients with moderately severe hypertension in whom the addition of as little as 50 mg. of hydralazine produced a 15-per cent further reduction in mean arterial pressure. This synergism with other antihypertensive agents was again illustrated in the good response in arterial pressure attained when daily doses of 100 mg. of hydralazine and 750 mg. of alpha-methyl-dopa were added to the chlorthalidone-reserpine combination in patients with severe hypertension. The potency of a daily dose of 100 mg. of hydralazine when added to this combination seemed to be equivalent to that of the blocking agents without producing the objectionable side effects of these latter agents. Where-as the long duration of action of the combination of chlorthalidone and reserpine is a real advantage allowing for once a day administration, the slow onset of action particularly that of reserpine may at times be a distinct disadvantage. When rapid reduction in arterial pressure is indicated as in patients with severe vascular disease, one should not rely on the combination of chlorthalidone and reserpine administered alone. Additional rapidly acting antihypertensive therapy must be instituted concurrently.

Although hyperuricemia developed in 88 (72 per cent) of the patients in this study, only eight (6 per cent) of the patients developed signs and symptoms of acute gouty arthritis. Unfortunately uric acid determinations were not routinely performed when the patients were receiving other thiazide diuretics. Comparable data are therefore not available on the incidence of hyperuricemia or of the development of gouty arthritis produced by other thiazide diuretics. It seems that the incidence of arthritis is not particularly related to the duration of administration or the degree of rise in uric acid but to the presence or absence of an inherited gouty trait. It is believed that the thiazide derivatives precipitate acute gouty arthritis only in those patients in whom a gouty tendency is present.10-12 The addition of colchicine and probenecid to the chlorthalidone-reserpine combination promptly controlled the gouty state in all but one of the patients. It is also thought that the continued use of these agents in patients who had a history of gout prevented the development of acute arthritis. It would seem, therefore, (1) that the development of gouty arthritis in patients receiving thiazide derivatives need not be an indication for discontinuation of the drug; (2) if arthritis develops during thiazide therapy, colchicine and probenecid should be administered promptly; and (3) these latter agents should be administered prophylactically to patients with a history of gout.

Although 11 patients who did not have a history of hyperglycemia prior to the study developed transient increases in blood glucose
during the study, discontinuation of the chlorthalidone-reserpine combination for 2 weeks was followed by return of the blood glucose to normal values. These data are not in accord with those of Wolff and Parmeley, who found a 33-per cent increase in blood glucose as compared to a 7.7-per cent increase in a control group. Admittedly, thiazide diuretics were used in their study, whereas chlorthalidone was utilized exclusively here. Although sufficient data on the patients studied here while they were on other thiazide diuretics are not available, it is our impression that chlorthalidone causes no greater incidence of hyperglycemia. In four of the 12 patients who were diabetic prior to the study, the 1-hour postprandial blood glucose was consistently elevated 40 to 60 mg. per cent above control values. Discontinuing the chlorthalidone-reserpine combination in each of these patients for a 2-week period was followed by return of the 1-hour postprandial blood glucose to control levels. It would seem from these findings that (1) the thiazide diuretics are not contraindicated in the presence of diabetes and (2) the severity of the diabetic state should not be assessed when the patient is receiving thiazide diuretics. These substances should be withdrawn for at least 2 weeks.

Summary

One hundred nine patients with moderately severe hypertension and 12 patients with severe hypertension received the combination of 50 mg. of chlorthalidone plus 0.25 mg. of reserpine combined in a single tablet (Regroton) administered once daily for an average duration of 2 years.

The ease of administration (one tablet daily), the effectiveness (78-per cent good response), the lack of development of drug resistance over a 2-year period, and the small incidence of side effects would seem to make the combination of 50 mg. of chlorthalidone plus 0.25 mg. of reserpine the ideal treatment for most patients with hypertension. If a more rapid reduction in arterial pressure is indicated, as in patients with severe hypertension, or if a satisfactory therapeutic response has not been observed in 3 to 4 months in patients with moderately severe hypertension, suboptimal doses of other antihypertensive agents may be added.

References


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