Evaluation of Chlorothiazide Alone in the Treatment of Moderately Severe and Severe Hypertension

By Frank A. Finnerty, Jr., M.D., Joachim H. Buchholz, M.D., John Tuckman, M.D., George T. Hajjar, M.D., and Gloria DeCarlo Massaro, M.D.

The effectiveness of alternate 6-month courses of chlorothiazide alone with standard antihypertensive therapy is compared in 11 patients with severe hypertension and 30 patients with moderately severe hypertension. These results are then compared with those of a 6-month combined treatment period when the patients received both chlorothiazide and standard antihypertensive therapy.

Although studies in many clinics have demonstrated the potentiation of antihypertensive agents by chlorothiazide,1–3 its value alone in patients with moderately severe and severe hypertension has not been established. This investigation was designed to compare the effectiveness of alternate 6-month courses of chlorothiazide alone with standard antihypertensive therapy, and to compare the results of these periods with those of a 6-month combined treatment period when patients received both chlorothiazide plus standard antihypertensive therapy.

Methods and Materials

Forty-one patients were chosen from the Hypertensive Clinic of the District of Columbia General Hospital, 11 with severe hypertension and 30 with moderately severe hypertension. The pertinent data are presented in tables 1 and 2.

Experimental Plan. Each patient was followed through 4 study periods. A 1-month no treatment period, a 6-month chlorothiazide period, a 6-month standard therapy period, and a 6-month combined therapy period. The only indication for not strictly adhering to this experimental plan was the presence of fulminating disease in some of the patients with severe hypertension that necessitated the addition of further therapy. In order to avoid the influence of climate, one half the patients of each group were started on the chlorothiazide period during the summer months and the other half during the winter months.

During the “no treatment period” and during the first 2 months of each of the other treatment periods the patients visited the clinic weekly. During the remainder of the study clinic visits were biweekly. At the beginning of the study all the patients underwent the routine clinical and laboratory studies, including a complete history and physical examination, urinalysis, blood urea nitrogen determination, electrocardiogram, and chest roentgenogram. These laboratory procedures were repeated during each study period.

The dose of chlorothiazide (Diuril) was 1 gm. a day (500 mg. twice a day) in all patients. The patients were allowed to eat a regular diet; supplemental potassium was not administered. During the period of standard therapy the patients with severe hypertension received mecamylamine (Inversine) and reserpine (Harmonyl). The daily dose of reserpine was 0.25 mg. The dose of mecamylamine was individualized and ranged between 15 and 36 mg. per day. During the period of standard therapy the patients with moderately severe hypertension received veratrum (Veriloid) and reserpine (15 patients) or hydralazine (Apresoline) plus reserpine (15 patients). The dose of reserpine was 0.25 mg. The dose of veratrum ranged between 9 and 16 mg. per day and the dose of hydralazine ranged between 200 and 300 mg. per day.
Soon after the beginning of the combined treatment period it was necessary to reduce the dose of mecamylamine in the patients with severe hypertension by one third to one half in order to avoid severe postural hypotension. If the level of arterial pressure did not increase following such a reduction in dosage an attempt was then made to substitute veratrum or hydralazine for the ganglionic-blocking agents. Similarly, in the patients with moderately severe hypertension chlorothiazide necessitated a reduction of dosage of both veratrum and hydralazine. If the level of arterial pressure did not increase in these patients, an attempt was made to discontinue hydralazine and veratrum.

**RESULTS**

**Severe Group**

**Standard Therapy vs. Chlorothiazide Therapy.** The results of the first part of this study are shown in table 3. A 9-per cent reduction in mean arterial pressure (MAP) resulted from both chlorothiazide and mecamylamine plus reserpine in 5 patients. In an additional 3 patients a 10-mm. reduction in mean arterial pressure occurred under chlorothiazide therapy. Despite the moderate reduction in mean arterial pressure in both groups there was no significant change in the severity of the vascular disease, e.g., fundi, heart, kidneys. A rising arterial pressure and the development of fresh retinal hemorrhages necessitated the addition of chlorothiazide to ganglionic-blocking therapy at the end of 2 months in 3 patients.

**Combination Therapy.** The data resulting from the addition of chlorothiazide to standard therapy are outlined in table 4. During the first 2 months of this period the dose of mecamylamine could be reduced by one half in all but 2 patients. Such combination therapy resulted in a 16-per cent reduction in mean arterial pressure below the no treatment level and a 7-per cent reduction below the lowest previous level. More important, however, was the reversal of papilledema in 3 patients, clearing of hemorrhages and exudates in 5 patients, and a decrease in heart size in 5 patients.

At the end of the fourth month of this period hydralazine in a daily dose of 300 mg. and veratrum in a daily dose of 9 mg. could be substituted for mecamylamine in 7 and 3 patients respectively. The excellent therapeutic results continue in these patients at the present time (5 months follow-up). Continued use of mecamylamine was necessary in 1 patient.

**Moderately Severe Group**

**Standard Therapy vs. Chlorothiazide Therapy.** The data from the chlorothiazide period are compared with those from the standard treatment period in table 5 where it can be noted that a comparable reduction in average arterial pressure occurred in both groups. Further analysis of these data shows that more than a 20-mm. reduction in mean arterial pressure followed both chlorothiazide alone and standard therapy in 13 patients, followed standard therapy alone in 4 patients, and followed chlorothiazide therapy alone in 2 patients. Expressed in a different way, it can be stated that standard therapy was successful in 17 patients (13 plus 4).
CHLOROTHIAZIDE AND HYPERTENSION

Table 3.—Severe Hypertensive Group—11 Patients

<table>
<thead>
<tr>
<th>Dose</th>
<th>No treatment—1 mo.</th>
<th>Chlorothiazide—6 mos. (1 Gm./day)</th>
<th>Meanamylamine + Reserpine—6 mos. (15-36 mg./day + 0.25 mg./day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure</td>
<td>170 ± 26.4 mm. Hg</td>
<td>153 ± 17.3 mm. Hg (9%↓)</td>
<td>155 ± 19.3 mm. Hg (9%↓)</td>
</tr>
<tr>
<td>Fundi</td>
<td>Grade III—8 pts. Grade IV—3 pts.</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Cong. failure</td>
<td>Minimal—3 pts.</td>
<td>Less—2 pts.</td>
<td>No change</td>
</tr>
<tr>
<td>ECG</td>
<td>L V H—9 pts.</td>
<td>Less—L V H—3 pts.</td>
<td>No change</td>
</tr>
<tr>
<td>RUN</td>
<td>24 mg. per cent (9-35)</td>
<td>No change</td>
<td>No change</td>
</tr>
</tbody>
</table>

Table 4.—Severe Hypertensive Group—11 Patients

<table>
<thead>
<tr>
<th>Dose</th>
<th>Chlorothiazide—6 mos. (1 Gm./day)</th>
<th>Meanamylamine + Reserpine—6 mos. (15-36 mg./day + 0.25 mg./day)</th>
<th>Meanamylamine + Reserpine—6 mos. (5-15 mg./day + 0.25 mg./day + 1 gm./day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure</td>
<td>153 ± 17.3 mm. Hg (9%↓)</td>
<td>15.5 ± 19.3 mm. Hg (9%↓)</td>
<td>143 ± 17.6 mm. Hg (16%↓)</td>
</tr>
<tr>
<td>Fundi</td>
<td>No change</td>
<td>No change</td>
<td>Grade IV→II—3 pts. Grade III→II—5 pts.</td>
</tr>
<tr>
<td>Cong. failure</td>
<td>Less—2 pts.</td>
<td>No change</td>
<td>Only satisfactory therapy—3 pts.</td>
</tr>
</tbody>
</table>

*By fourth month 300 mg. hydralazine or 9 mg. veratrum could be substituted for meanamylamine in 10 of 11 patients.

and chlorothiazide was successful in 15 patients (13 plus 2) or 50 per cent of the patients with moderately severe hypertension.

Combined Treatment Period. The data resulting from the addition of chlorothiazide to standard treatment in the 30 patients with moderately severe hypertension are presented in table 6. The addition of chlorothiazide to either veratrum or hydralazine resulted in a 17-per cent reduction in mean arterial pressure as compared to the no treatment level and an 8-per cent reduction in mean arterial pressure below the lowest previous treatment level. In each patient the addition of chlorothiazide resulted in more than a 10-mm. reduction in mean arterial pressure below the lowest previous level. Such combination therapy also resulted in complete clearance of congestive heart failure present in 3 patients. The addition of chlorothiazide permitted reduction in the dosage of hydralazine in 12 of 15 patients and a reduction in dosage of veratrum in 13 of 15 patients. During the last 2 months of the combined treatment period it was possible to discontinue hydralazine in 10 patients and veratrum in 13 patients, chlorothiazide plus reserpine serving as the sole antihypertensive agents. The excellent therapeutic results continue in these patients at the present time (5 months follow-up).

Discussion

Neither chlorothiazide alone nor ganglionic-blocking agents plus reserpine represented effective treatment in the patients with severe
hypertension presented here. The inability of ganglionic-blocking agents to control the accelerated phase of hypertension was not in keeping with prior experience in this clinic. Although toxic reactions were frequent with ganglionic-blocking agents, the accelerated phase of hypertension could usually be reversed. The poor results obtained in the patients presented here must be interpreted as indicating fulminating vascular disease. It was noteworthy, therefore, that the addition of chlorothiazide to ganglionic-blocking agents plus reserpine produced excellent results in all these patients. It would seem, therefore, that in the absence of uremia, such combination therapy should be instituted promptly when the accelerated phase of hypertension is present. Time need not be wasted in administering either drug separately.

The potentiation of the antihypertensive properties of mecamylamine by chlorothiazide made it necessary to reduce the dosage of mecamylamine to avoid severe postural hypotension. Although the reduced dose of mecamylamine avoided postural hypotension, undesirable side effects such as blurred vision, fatigue, and impotency still remained. It was noteworthy that when the accelerated phase of hypertension had been halted, i.e., papilledema had cleared, flame-shaped hemorrhages regressed, and the level of arterial pressure had been lowered, hydralazine or veratum could be successfully substituted for mecamylamine.

It must be admitted that the continued good therapeutic response noted when these latter agents were substituted for ganglionic-blocking agents might not have been entirely due to these drugs. Studies in this laboratory have shown that acute reduction of arterial pressure with any agent in patients in an accelerated phase of hypertension has frequently been associated with a long period of hypertension, longer than can be accounted for by the action of the drug itself. Following acute therapy the arterial pressure frequently does not return to control levels for 6 to 8 weeks. Similarly, clinical experience attests to prolonged periods of hypotension following an acute insult to the circulation such as myocardial infarction or a cerebral vascular accident. It is as though a cycle has been interrupted or the barostat of arterial pressure has been set at a lower level. Whatever the reason for the continued good response in the patients presented here, long-term ganglionic-blocking therapy was seldom indicated. Reserving ganglionic-blocking therapy for the short-term treatment of the accelerated phase of hypertension will not only free the patient from uncomfortable side effects but will also insure sensitivity to ganglionic-blocking agents that may be life-saving at a later date.

Although chlorothiazide alone has no place in the treatment of severe hypertension, one might argue from the studies presented here that it is as effective as veratum plus reserpine or hydralazine plus reserpine in patients with moderately severe hypertension. Its ease

<table>
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<tr>
<th>Drug Combination</th>
<th>Dose</th>
<th>Mean arterial pressure</th>
</tr>
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<tbody>
<tr>
<td>Chlorothiazide–6 mos.</td>
<td>1 Gm./day</td>
<td>143 ± 21.5 mm. Hg (9%↓)</td>
</tr>
<tr>
<td>Veratum–15 pts. + Reserpine (6 mos.) or Hydralazine–15 pts.</td>
<td>Veratum–9–16 mg./day Hydralazine–200–300 mg./day Reserpine–0.25 mg./day</td>
<td>145 ± 16.4 mm. Hg (9%↓) 132 ± 17.3 mm. Hg (17%↓)</td>
</tr>
</tbody>
</table>

*By fourth month veratum and hydralazine could be discontinued in 10 and 13 patients respectively.
of administration—no need for individual titration of dosage, the almost complete absence of side effects, and the lack of drug resistance seem to make chlorothiazide the drug of choice in this regard. Since chlorothiazide alone was effective in only one half of the patients with moderately severe hypertension and, since the combination of chlorothiazide plus hydralazine or veratrum was effective in all of the patients with moderately severe hypertension, there would seem to be no indication to administer these agents separately. The potentiation of the antihypertensive properties of veratrum and hydralazine by chlorothiazide enables lower doses of these agents to be used, thus practically doing away with side effects.

Past experience with both hydralazine and particularly veratrum attests to the frequent development of drug resistance when these agents are used for long periods of time. It is important, therefore, that once a hypotensive effect had been attained with veratrum or hydralazine in the patients with moderately severe hypertension that these agents could be withdrawn and antihypertensive therapy continued with reserpine plus chlorothiazide. Again it might be argued that the continued good therapeutic effect in these patients was not a direct consequence of chlorothiazide plus reserpine but merely represented a quiescent phase of the hypertensive state. Those who think that reserpine administered by mouth possesses no antihypertensive properties would probably choose this latter interpretation.

It is suggested from these studies that the choice of the antihypertensive agent should change with the severity of the hypertensive state. Whereas ganglionic-blocking agents plus chlorothiazide are needed to control the accelerated phase of hypertension initially, once this phase has been controlled, less potent therapy may be substituted. It seems useful in this regard to divide antihypertensive therapy into 2 phases: initial and maintenance. Initial therapy in the accelerated phase of hypertension should include ganglionic-blocking agents, chlorothiazide, and reserpine. Following control of the accelerated phase (clearing of papilledema and retinal hemorrhages) veratrum or apresoline may be substituted for the ganglionic-blocking agents. In patients with moderately severe hypertension initial therapy consists of veratrum or apresoline plus chlorothiazide plus reserpine. Long-term maintenance therapy, which may be instituted when the arterial pressure has been stabilized for 2 or 3 months, consists of chlorothiazide plus reserpine.
Summary

Neither chlorothiazide alone nor ganglionic-blocking agents plus reserpine represented effective treatment in the 11 patients with severe hypertension studied here. The addition of chlorothiazide to ganglionic-blocking agents plus reserpine reversed the accelerated phase of hypertension in each of these patients. Once papilledema had cleared and retinal hemorrhages had regressed, it was possible to substitute hydralazine or veratrum for the ganglionic-blocking agents in these patients.

Chlorothiazide alone and veratrum or hydralazine plus reserpine were both found effective in controlling 50 per cent of the patients with moderately severe hypertension. The addition of chlorothiazide to either of these agents resulted in satisfactory control of the arterial pressure in all the patients with moderately severe hypertension. Once a hypotensive effect had been attained with veratrum or hydralazine, these agents could be withdrawn and antihypertensive therapy continued with reserpine plus chlorothiazide.

Summario in Interlingua

Ni chlorothiazido sol ni agentes de blocage ganglionic in combination con reserpina eseva efficace como medication in le 11 patientes con sever hypertension qui es hic studiate. Le addition de chlorothiazido a agentes de blocage ganglionic e reserpina reverteva le phase accelerate de hypertension in omne iste patientes. Post que le papilledema se habeva resolvite e post que le hemorrhagias retinal habeva regredite, il esseva possibile in iste patientes reimplaciar le agentes de blocage ganglionic per hydralazina o veratrum.

Chlorothiazido sol e veratrum o hydralazine in combination con reserpina se mostrava ambes efficace in le stabilisation del processo pathologic de 50 pro cento del patientes con hypertension de grados moderate mente sever. Le addition de chlorothiazido a iste agentes individual resultava in un satis facente stabilisation del tension arterial in omne le patientes con hypertension de grados moderate mente sever. Post que un effecto hypotensive habeva essite establite per medio de veratrum o hydralazina, iste agentes po teva esser eliminate, e le therapia antihyper tension poteva esser continue con reserpina in combination con chlorothiazido.

References


Hence it sometimes happens that, when the lumen of some artery has been too long obstructed or ligated, the blood busies itself in opening a wider channel for its passage in this vessel, must drive and buffet all the more into the next ones, until it has considerably dilated them to give itself room.—Richard Lower, Tractatus de Corde, 1669.
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Circulation. 1959;20:1037-1042
doi: 10.1161/01.CIR.20.6.1037

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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