Hemodynamic and Hypotensive Effects of Long-term Therapy with Chlorothiazide

By James Conway, M.D., Ph.D., and Philip Lauwers, M.D.

Long-term treatment of hypertension with chlorothiazide alone produces moderate reduction in blood pressure in 66 per cent of patients with hypertension. This fall in pressure is due to a reduction in total peripheral resistance rather than a fall in cardiac output.

The value of any drug in the treatment of hypertension rests in the last analysis on the frequency and magnitude of its depressor effect on the blood pressure and upon whether it corrects the elevated peripheral resistance, characteristic of essential hypertension. Although the hypotensive action of chlorothiazide has been previously studied,1-3 no attempt has yet been made to determine its usefulness in a large number of unselected hypertensive patients.

This report investigates the over-all effectiveness of long-term therapy with chlorothiazide in hypertension and studies the hemodynamic mechanism by which this treatment reduces the blood pressure.

Methods

Clinical Observations

After preliminary cardiac and renal investigations, 83 unselected ambulatory patients with hypertension were given chlorothiazide as the sole hypotensive medication. None of these patients was edematous but 16 previously had had a splenectomy that had not been successful in reducing the blood pressure. The usual maintenance dose of chlorothiazide was 0.5 Gm. twice daily after an initial 3-day period of 1 Gm. twice daily. In 5 patients a larger dose of 2 Gm. per day was administered continuously. Patients were urged to reduce sodium intake by avoiding salty foods and by eliminating salt from cooking and at the table. In 14 patients blood pressure readings were taken twice daily at home and in the remainder readings were taken in the clinic. Treatment was maintained for at least 1 month in all subjects, with the exception of 7 patients who had not responded after 2 weeks and whose clinical condition required the use of more potent drugs. At varying periods after the first month of treatment the remaining patients who failed to respond were withdrawn from the investigation to be given other drugs. The average duration of therapy for the entire group was 5.4 months.

Hemodynamic Observations

Hemodynamic studies were undertaken on 23 hypertensive out-patients in whom there was no clinical evidence of cardiac or renal failure and none had malignant hypertension. Plasma volume was measured in 10 patients and cardiac output in 16. Control observations were usually performed before starting treatment, but in 1 of the plasma-volume group and 4 of the cardiac-output group, chlorothiazide was administered first and was thereafter withdrawn or replaced by a placebo for a period of 1 month before the control observations were made. All these patients received the same dose of chlorothiazide, 1 Gm. per day, for at least 1 month before its effect was determined.

In order to study the early effects of the drug, these investigations were also performed on 7 patients before and within the 3 weeks of starting treatment. Cardiac output was measured in 4 subjects and plasma volume in 4 also.

Plasma volume was estimated by the dye-dilution method with Evans blue.4 The total dose, which varied from 15 to 25 mg., was measured by weighing the syringe before and after each injection. After the subject had been lying down for half an hour and a control sample of blood had been drawn, the dye was injected into the antecubital vein. The needle was flushed with 5 ml. of saline before and after the injection. After 15 minutes had elapsed to allow for intravascular mixing, 4 samples of blood were drawn, without venous congestion, at 5-minute intervals from an indwelling needle in the antecubital vein of the opposite arm. Hematocrit determinations were made on the second and fourth samples of blood. The concentration of Evans blue in the plasma was measured,

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Table 1

Effect of Chlorothiazide on the Blood Pressure in Patients with Various Clinical Types of Hypertension

<table>
<thead>
<tr>
<th>Type of hypertension</th>
<th>No. of cases</th>
<th>Blood pressure (mm. Hg)</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Before treatment</td>
<td>On chlorothiazide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systolic</td>
<td>Diastolic</td>
</tr>
<tr>
<td>Essential</td>
<td>59</td>
<td>188</td>
<td>116</td>
</tr>
<tr>
<td>Post-splanchenecotomy</td>
<td>16</td>
<td>190</td>
<td>128</td>
</tr>
<tr>
<td>Malignant</td>
<td>4</td>
<td>222</td>
<td>126</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>4</td>
<td>217</td>
<td>129</td>
</tr>
</tbody>
</table>

Direct blood pressure recordings were obtained before and after each dye-curve with a Statham P23A strain-gage connected to the polyethylene tubing. The mean pressure was obtained electrically by the insertion of a capacitor in the circuit. Thus it was possible to determine the cardiac output by the Stewart-Hamilton formula. This, with the mean blood pressure taken almost simultaneously, was used to calculate the total peripheral resistance according to the formula:

$$TRP = \frac{Mean\ BP \times 60 \times 1332}{cardiac\ output \times 1000} \text{ dynes sec. cm}^{-2}$$

The serial measurements of cardiac output in the recumbent posture without premedication frequently showed variation of ± 600 ml. per minute from one estimation to the next. As a rule these changes were accompanied by simultaneous changes in heart rate and blood pressure and the first cardiac output determination was usually higher than subsequent ones. The average of observations recorded at a single session were then divided by the patient's surface area to give the cardiac index in liters per minute.

Results

Clinical Observations

To determine the frequency with which chlorothiazide affected the blood pressure in the group of 83 patients, it was arbitrarily decided that a reduction in pressure of at least 10 per cent in both systolic and diastolic levels would constitute a satisfactory response. According to this standard there were 55 responders (66 per cent) and 28 non-responders. Age, sex, or degree of cardiac involvement did not affect the frequency of response to the drug but all the patients in the malignant or accelerated phase and those with renal azotemia failed to show a fall in blood pressure (Table 1). The average blood

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photometrically at a wavelength of 620 mμ with a Beckman spectrophotometer. The dilution of Evans blue in plasma was estimated by extrapolation to zero time of the slope of the time-concentration curve of the 4 samples of plasma. Repeated observations in the same patient by this method gave values which were within 3 per cent of each other.

Cardiac output was measured by the dye-dilution technic with the patient in a recumbent position and without preliminary sedation. Indigo-carmine was used as the indicator and injections were made through a needle lodged in the antecubital vein of the right arm, which was elevated well above the heart level by 3 pillows. The dye was flushed into the vein by 5 to 10 ml. of saline and the amount of dye delivered was estimated by weighing the syringes before and after injection. The total dose varied from 34 to 42 mg. For sampling blood and recording blood pressure, a thin-walled 20-gage needle was placed in the brachial artery of the opposite arm under local anesthesia. The needle was connected by 10 cm. of polyethylene tubing to a cuvette densitometer with filters at 620 mμ. To inscribe the dilution curve the blood was drawn through the recording instrument at a rate of 25 to 30 ml. per minute by means of a motor-driven syringe. Photographic recordings were made with gain of the instruments arranged to give a deflection of approximately 2 cm. for 1 mg. per liter of dye. The dye-dilution curves were calibrated by drawing duplicate samples of the patient's blood containing known concentrations of dye through the densitometer immediately after the procedure. Since indigo-carmine is rapidly excreted by the kidneys, it was possible to repeat the estimations of cardiac output at each session. Three determinations were usually made in each subject in the control state and again following therapy with chlorothiazide.

*Gilford Instrument Laboratory, Elyria, Ohio.
**Research recorder and camera by Electronics for Medicine, White Plains, N. Y.
pressure of the nonresponders was a little higher than responders; 205/122 and 185/115 mm. Hg, respectively. On the other hand patients who had undergone splanchnicectomy were unusually responsive; 12 of 16 exhibited a significant fall in pressure (table 1).

In patients with essential hypertension, the average fall in blood pressure was 26/17 mm. Hg. Consequently if the diastolic pressure is approximately 110 mm. Hg, it is probable that chlorothiazide will lower the blood pressure to normal. In our group there were 32 patients with this level of pressure and 17 were restored to normal pressure.

**Hemodynamic Studies**

The average control value for plasma volume in 10 patients was 2,673 ml., and after treatment with chlorothiazide, 2,582 ml. (fig. 1). When significant changes in plasma volume did occur, they were reflected in the appropriate directional changes in the hematocrit (table 2, fig. 1). The average fall in plasma volume of 90 ml. was considered to be of little physiologic consequence; nevertheless, the possibility remained that reduction in pressure could be brought about by a fall in cardiac output.

The cardiac index for the group of 16 hypertensive subjects varied between 2.6 and 5.1 L. per minute. This range was similar to that found in hypertensive patients by others and in normal subjects studied in this laboratory under similar conditions. The average pretreatment value of 3.7 L. per minute increased to 4.1 L. per minute after treatment with chlorothiazide (table 3, fig. 2). During this time the average blood pressure measured directly from the brachial artery fell by 38.6 mm. Hg systolic and 19.6 mm. Hg diastolic. Since the cardiac output remained relatively unchanged, the fall in pressure reflected a similar decline in total peripheral resistance, from 1655 to 1259 dynes sec. cm.-5 (table 3, fig. 2).

Three patients demonstrated a definite fall in cardiac output. In 2 of these patients the output change was more than adequate to account for the fall in blood pressure and the total peripheral resistance was increased. In 1 of these patients (Fe, table 3), the cardiac output determination was repeated after a further period of therapy with chlorothiazide. At this time, the cardiac index remained depressed, but the blood pressure had fallen further and peripheral resistance had returned to the pretreatment level.

Since these findings were at variance with those previously reported in hospitalized patients given chlorothiazide for shorter periods, plasma volume and cardiac output determinations were made before and after chlorothiazide had been administered for 5 to 19 days in 7 patients (table 4). In contrast to our previous findings, these patients exhibited a considerable fall in plasma volume (average 399 ml.) and in cardiac index (average 1.0 L. per minute) (table 4).

**Discussion**

**Effect of Chlorothiazide on the Blood Pressure**

The clinical usefulness of chlorothiazide has been somewhat overshadowed by the ability of this drug to enhance the effectiveness of other hypotensive drugs. It is particularly satisfying to observe that two thirds of the patients with hypertension respond to chlorothiazide alone and that in 50 per cent of the milder cases, with diastolic pressures
Table 2

Effect of Chlorothiazide Therapy on the Plasma Volume and Hematocrit

<table>
<thead>
<tr>
<th>Patient</th>
<th>Duration of treatment (days)</th>
<th>Plasma volume (ml)</th>
<th>Hematocrit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yo</td>
<td>0</td>
<td>2001</td>
<td>54.93</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>1850</td>
<td>55.91</td>
</tr>
<tr>
<td>Zi</td>
<td>0</td>
<td>3164</td>
<td>47.18</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>3445</td>
<td>45.15</td>
</tr>
<tr>
<td>Se</td>
<td>0</td>
<td>4000</td>
<td>53.44</td>
</tr>
<tr>
<td></td>
<td>42</td>
<td>3602</td>
<td>53.99</td>
</tr>
<tr>
<td>Le</td>
<td>0</td>
<td>2364</td>
<td>44.29</td>
</tr>
<tr>
<td></td>
<td>49</td>
<td>2847</td>
<td>43.74</td>
</tr>
<tr>
<td>Ca</td>
<td>0</td>
<td>3263</td>
<td>45.7</td>
</tr>
<tr>
<td></td>
<td>32</td>
<td>3271</td>
<td>45.45</td>
</tr>
<tr>
<td>Gu</td>
<td>0</td>
<td>1921</td>
<td>43.74</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>1603</td>
<td>46.61</td>
</tr>
<tr>
<td>Ly</td>
<td>0</td>
<td>2967</td>
<td>52.23</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>2851</td>
<td>54.32</td>
</tr>
<tr>
<td>Ba*</td>
<td>0</td>
<td>2500</td>
<td>49.38</td>
</tr>
<tr>
<td></td>
<td>43</td>
<td>2257</td>
<td>49.71</td>
</tr>
<tr>
<td>Au*</td>
<td>0</td>
<td>2100</td>
<td>43.48</td>
</tr>
<tr>
<td></td>
<td>39</td>
<td>2000</td>
<td>44.07</td>
</tr>
<tr>
<td>Bu*</td>
<td>0</td>
<td>2450</td>
<td>37.38</td>
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<td></td>
<td>35</td>
<td>2320</td>
<td>39.29</td>
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<tr>
<td>Mean</td>
<td></td>
<td>2673</td>
<td>47.07</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>2583</td>
<td>47.82</td>
</tr>
<tr>
<td>Change</td>
<td>—</td>
<td>—90</td>
<td>+0.75</td>
</tr>
</tbody>
</table>

These patients were also studied in the cardiac output series.

Below 110 mm. Hg, it is possible to restore the pressure to normal. The proportion of patients responding to the drug and the magnitude of the hypotensive effect which we have observed is higher than that reported by others.3, 13, 14 This discrepancy may be explained by the fact that a number of our patients had had a splanchecotomy which, although unsuccessful in itself, made the patients more sensitive to chlorothiazide.1

Since the chlorothiazide compares well in effectiveness with other hypotensive drugs, it is our practice to initiate therapy with chlorothiazide alone in all patients with normal renal function. In the absence of signs indicating urgency in the reduction of pressure we find it advisable to continue such treatment for 1 or 2 months.
LONG-TERM CHLOROTHIAZIDE

Effect of chlorothiazide therapy on mean blood pressure, cardiac index, and peripheral resistance in 16 patients. OFF = control observations without treatment; ON = after at least 28 days of treatment.

Mode of Action

During the initiation of chlorothiazide therapy, there is a fall in body weight and an associated loss of extracellular fluid volume and of plasma volume. As a result, cardiac output falls. Our data confirm this and differ from those of Aleksandrow et al., who found no change in cardiac output after 5 days of chlorothiazide therapy. Since restoration of plasma volume by the infusion of dextran will restore the blood pressure to its previous level, it seems undeniable that the initial fall in blood pressure is the simple hemodynamic consequences of oligemia. From the functional point of view this state is not entirely satisfactory, since calculated peripheral resistance rises and blood pressure reduction is achieved at the expense of blood flow to the tissues.

In contrast, long-term therapy with chlorothiazide appears to maintain the reduction in blood pressure by different means; plasma volume is restored toward normal and cardiac output returns to its previous level while the blood pressure reduction continues. This change is physiologically more satisfactory, since it shows that this drug eventually produces a functional reversal of the increased arterial resistance characteristic of hypertension.

The reason for this change in the mode of action of the drug is not evident. It may be due to a separate action of the drug that develops more slowly or to a readjustment of the peripheral resistance in response to the earlier oligemic phase. Another possibility, suggested to us by Dr. Freis, is that the later stage may result from the gradual improvement in the underlying hypertensive disease process brought about by the reduction of blood pressure, a mechanism similar to that suggested by Perry and Schroeder after long-term therapy with hexamethonium and hydral-

Table 4

<table>
<thead>
<tr>
<th>Name</th>
<th>Duration of Treatment (days)</th>
<th>Mean Blood Pressure (mm. Hg)</th>
<th>Plasma Volume (ml.)</th>
<th>Cardiac Index (L/min.)</th>
<th>Total Peripheral Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co</td>
<td>0</td>
<td>144*</td>
<td>2296</td>
<td>2.9</td>
<td>2038</td>
</tr>
<tr>
<td>Ho</td>
<td>8</td>
<td>135</td>
<td>1986</td>
<td>3.1</td>
<td>1407</td>
</tr>
<tr>
<td>Ha</td>
<td>6</td>
<td>141*</td>
<td>3420</td>
<td>2.9</td>
<td>2344</td>
</tr>
<tr>
<td>Jo</td>
<td>10</td>
<td>149</td>
<td>1015</td>
<td>3.2</td>
<td>1726</td>
</tr>
<tr>
<td>Au</td>
<td>12</td>
<td>148</td>
<td>5780</td>
<td>2.2</td>
<td>2351</td>
</tr>
<tr>
<td>Re</td>
<td>10</td>
<td>170</td>
<td>114</td>
<td>3.3</td>
<td>1573</td>
</tr>
</tbody>
</table>

Mean 11 | 132 | 3738 | 3.7 | 1681 | 2.7 | 1926 |

Change % | -10.5 | -10.7 | -21.7 | +14.6 |

*In these patients the blood pressure was measured indirectly and mean pressure estimated as diastolic pressure plus 1/3 of the pulse pressure.
azine. It is difficult to choose between these alternatives; but we would favor the concept of a distinct action of chlorothiazide, either direct or indirect, on the blood vessels. The reasons for this are that the period of approximately 1 month is too short a time to effect a reversal of the hypertensive process. Although ganglion blockers reduce cardiac output, long-term therapy does not lead to a fall in peripheral resistance. Furthermore, the continuing antihypertensive effect of chlorothiazide may be demonstrated by the elevation in pressure that occurs when the drug is withdrawn. Finally the gradual restoration of plasma volume and exchangeable sodium shows clearly that the equilibrium, which is finally reached between the diuretic effect of the drug and the homeostatic mechanisms, differs considerably from the initial oligemic state.

The nature and distribution of the change in peripheral resistance have yet to be determined before the true value of chlorothiazide therapy can be assessed. Whatever the final mechanism of action turns out to be, this study points out once again the need for studying the peripheral vascular bed in searching for the cause or cure of hypertension.

Summary

The value of long-term therapy with chlorothiazide as the sole antihypertensive drug has been investigated in 83 patients with hypertension. A significant fall in blood pressure was found to occur in 66 per cent of patients; the average reduction in pressure in patients with essential hypertension was 26/17 mm Hg.

After 1 or 2 weeks of therapy the plasma volume and cardiac output fell and total peripheral resistance increased.

After 1 month or more of continued treatment plasma volume and cardiac output were restored to pretreatment levels while the fall in blood pressure was maintained. Long-term therapy has therefore produced an action on the peripheral vessels leading to a reduction in total vascular resistance.

Summario in Interlingua

Le valor del uso de chlorothiazido como sol agent in antihypertensive in therapia a longe vista esseva investigate in 83 patientes con hypertension. Esseva trovata que un grado significative de reduction del tension de sanguine occurreva in 66 pro cento del casos. Le reduction medie del tension en patientes con hypertension essential amonta a 26/17 mm de Hg.

Post 1 o 2 septimanas de therapia, le volumen del plasma e le rendimento cardiae descendeva e le total resistentia peripherie montava.

Post 1 mense o plus de tractamento continue, le volumine del plasma e le rendimento cardiae esseva restaurate al nivelos pretracetental durante que le reduction del tension de sanguine esseva mantenite. Le conclusion es que le therapia a longe vista con chlorothiazido exereeva un effecto super le vasos peripherie que resultava in un reduction del total resistentia vascular.

Acknowledgment

We would like to acknowledge the generous and enthusiastic help of Dr. S. W. Hoobler throughout this study, and to thank Dr. J. Beem, of Merck, Sharp and Dohme, for the supplies of chlorothiazide used in this study.

References

LONG-TERM CHLOROTHIAZIDE


Medical Eponyms

By Robert W. Buck, M.D.

Pardee's Sign. Harold E. B. Pardee (b. 1886) Assistant Professor of Clinical Medicine at the Cornell University Medical College described "An Electrocardiographic Sign of Coronary Artery Obstruction" in the Archives of Internal Medicine 26:244-257 (August) 1920.

"It is hoped to show that obstruction of a branch of the coronary artery is followed by a sign which is characteristic of this condition and is readily recognizable in the human electrocardiogram. . . . The characteristic changes appearing a day or two after the obstruction are as follows: The QRS group is usually notched in at least two leads, and usually shows left ventricular preponderance. The T wave does not start from the zero level of the record in either Lead I or Lead III though, perhaps, from a level not far removed from it, and in this lead quickly turns away from its starting point in a sharp curve, without the short straight stretch which is so evident in normal records preceding the peak of the T wave. The T wave is usually downward in Lead II and in one other lead. Not all of these changes are to be found in every record, but enough of them are present to give it a characteristic appearance."

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