A Mechanism of Chlorothiazide-Enhanced Effectiveness of Anti hypertensive Ganglioplegic Drugs

By Harriett P. DusTAN, M.D., G. R. Cumming, M.D., A. C. Corcoran, M.D., and Irvine H. Page, M.D.

Chlorothiazide decreases plasma volume, heart size, and cardiac output. The oligemia stimulates vasomotor tone; this tends to maintain arterial pressure because chronic arterial hypertension is characteristically self-sustaining and homeostatic. This oligemic stimulation of vasomotor tone results in increased sensitivity to the antihypertensive effect of drugs depressing or blocking vasomotor function.

A PRELIMINARY report,1 on chlorothiazide-induced sensitization to the hypotensive effect of antihypertensive ganglioplegic drugs, described an association between the sensitization and reduction of plasma volume, and suggested that this depletion might be the primary mechanism. Other possible mechanisms were not excluded.

In the previous study we had anticipated that the depressor response to “bloodless phlebotomy” would be intensified during chlorothiazide treatment. Such an intensification was not found, and this seemed inconsistent with the concept of oligemia as the primary mechanism. However, Dr. James McCubbin, of this Division, suggested that the seeming paradox might be explained by increase in vasomotor activity that occurs during oligemia2,3 and, further, that increased vasomotor tone would also account for the enhanced responsiveness to ganglioplegic drugs such as occurs in the neurogenic hypertensive dog.4

This report describes experiments in which this concept was tested by indirect methods. The results are consistent with the concept.

METHODS

The effects of chlorothiazide on cardiac output, blood pressure, and total peripheral resistance were studied in 11 hospitalized hypertensive patients.5 The effects of “prolonged” administration were studied in 9 patients who received 1 Gm. of chlorothiazide5 twice daily for periods ranging from 4 to 6 days, and effects of intravenous administration were studied in 2 patients who were given 500 mg. In the prolonged study, hemodynamic measurements were made before and at the end of the period of drug treatment, except in 3 patients in whom the sequence of observations was reversed. In the 2 patients who were studied after intravenous administration, measurements were made immediately before and 1 hour after the injection. One patient continued to take 200 mg. of hydralazine daily; the remaining patients received no vasoactive drugs during the period of chlorothiazide administration. To investigate further the enhanced responsiveness to ganglioplegic drugs induced by chlorothiazide, 7 patients were given tetraethylammonium chloride (TEAC) intravenously immediately after the control and “drug” observations had been made. Each patient received 5 mg./Kg. at a rate of 1 mg./Kg./min.; 5 and 15 minutes after the injection, cardiac output and blood pressure measurements were repeated. The effects of an infusion of 500 ml. of dextran were studied in 1 who was not given TEAC. Throughout the period of investigation blood pressure was measured 4 times daily in the supine and standing positions. In addition, heart size was determined in 12 patients from telerentgenograms during both the control and “drug” periods. Six of these patients were from this study group. The remaining 6 were similarly treated during a study of chlorothiazide-induced changes in renal function.6 Serum electrolytes were measured in most patients.

Cardiac output was determined in the supine position after a fast of at least 8 hours, by a dye-dilution technic with indigo carmine.6 Dye was injected from a calibrated 5-ml. syringe into the antecubital vein and this was followed immediately

*Kindly supplied by Dr. John R. Beem, Merck Sharp & Dohme.
by an injection of 8 ml. of saline. The curve of
dye concentration was obtained by drawing brachial arterial blood through a cuvet densitometer by means of a constant flow system. The curve was calibrated by timed collection of a pooled sample. Dye concentration of the plasma of the pooled sample was measured in a Coleman 6A spectrophotometer at 600 μ. Intraarterial pressure was measured with a strain gage and a Sanborn direct-writing recorder. Mean blood pressure (MBP) was obtained from the recording by planimetry. Mean circulation time (MCT) was calculated from the formula $MCT = C \times t/C$, and central blood volume (CBV) from the formula $CBV = MCT \times CO$ (cardiac output). In 6 patients the control studies were carried out before chlorothiazide was given, while in the remaining the sequence was reversed and control values were obtained after discontinuance of the drug.

Plasma volume was estimated from the volume of distribution of radio-iodinated serum albumin.

### RESULTS

#### Changes Induced by Prolonged Administration of Chlorothiazide

#### Cardiac Output and Related Functions

The effects of the prolonged administration of chlorothiazide on cardiac output and related functions were studied in 9 patients (table 1). In 7 cases control values for cardiac index (cardiac output in L./min./M.^2) represent averages of 2 determinations (within 10 minutes). The variations between means of the 2 measurements averaged 4.7 per cent. Control values were within normal limits, averaging 3.2 L./min./M.^2. In all patients output diminished after several days of chlorothiazide administration. The decreases ranged from 11 to 42 per cent (mean 23). Mean arterial pressure (MBP), calculated

### Table 1

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<th>Patient</th>
<th>C.I. (L./min./M.^2)</th>
<th>MBP (mm. Hg)</th>
<th>TPR dynes/ sec./cm.^{-1}</th>
<th>CBV (ml.)</th>
<th>PV (ml.)</th>
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<td>167/105</td>
<td>149/101</td>
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</table>

| Percentile changes | -23 | -6 | +23 | -21 | -14 | -3 | -11 | -8 | -13 | -10 |

* C.I., cardiac index. MBP, mean blood pressure. TPR, total peripheral resistance. CBV, central blood volume. C, control observations. D, chlorothiazide observations. PV, plasma volume.

*Colson Corporation, Elyria, Ohio.
HEMODYNAMIC RESPONSES TO TEAC
(Mean for 6 patients)

CONTROL

CHLOROTHIAZIDE

CL

L/min

30

20

10

MBP

mm Hg

150

125

100

75

TPR

dynes/sec/cm²

2500

2000

1500

CONTROL

5 min

15 min

CONTROL

5 min

15 min

Fig. 1 Left. Means of observations of the effects of TEAC on cardiac output (stated here as CI), mean blood pressure, and total peripheral resistance before and after administration of chlorothiazide, with enhanced depressor response after chlorothiazide and a decreased rather than an increased total peripheral resistance.

Fig. 2 Right. Decrease in cardiac output and increase in total peripheral resistance as the result of 6 days' treatment with chlorothiazide and return of these functions to control levels over the course of 30 minutes' infusion of dextran. Pretreatment mean blood pressure 138 mm. Hg, after chlorothiazide 140 mm. Hg, at the end of dextran infusion 150 mm. Hg.

from measurements made at the time of the output determination, was lower in 6 of the 9 patients after chlorothiazide, and was unchanged in 3. The calculated total peripheral resistance during the control study averaged 2,072 dynes/sec./cm.², and at the end of the experimental period was increased in 8 by a mean of 27 and decreased in 1 by 10 per cent. Central blood volume decreased by a mean of 21 per cent. Mean circulation time was prolonged in 4 of the 9 patients.

Plasma Volume. This measurement was made in 7 patients, and consistent decreases averaging 14 per cent were observed after chlorothiazide.

Responses to TEAC. In 6 of the 7 patients tetraethylammonium chloride (TEAC) had consistent effects (fig. 1). In both test situations (without or during chlorothiazide) TEAC injections were followed by decreases in cardiac output (CI) which averaged 16 per cent less than the pre-injection values. Blood pressure changes were transient during the control study; mean blood pressure was decreased by a mean of 11 mm. Hg at 5 minutes after injection, and returned to pre-injection levels at 15 minutes. Chlorothiazide treatment intensified the blood pressure response to TEAC; at 5 minutes mean blood pressure decreased by a mean of 31 mm. Hg and did not return to the pre-injection values in 15 minutes. Total peripheral resistance during the control study rose after TEAC injections. During chlorothiazide treatment total peripheral resistance was elevated and TEAC then caused a slight fall at 5 minutes, but by 15 minutes the values returned to pre-injection levels. In the 1 patient TEAC increased cardiac output and decreased arterial pressure both with and without chlorothiazide.

Infusion of Dextran. To explore the possibility that decreases in cardiac output during chlorothiazide administration were due to hypovolemia, 1 patient, who had been given chlorothiazide for 6 days and had sustained a 16 per cent decrease in cardiac output, was given 500 ml. of dextran intravenously (fig. 2). This infusion was started immediately after the determination of cardiac output; it was given at a rate of 15 ml./min.; output measurements were repeated after 300 ml. and 500 ml. of dextran had been given. The initial infusion of dextran increased blood pressure and cardiac output and decreased
total peripheral resistance; at the time of the second measurement, cardiac output was restored to, and blood pressure was greater than, the pre-treatment level.

Other Observations. Serum electrolytes were measured before and during chlorothiazide administration. Serum sodium fell an average of 6 mEq./L., potassium 0.6 mEq./L., chloride 4 mEq./L., while CO₂ content increased by 3.8 mEq./L. All patients lost weight; these losses averaged 3.0 per cent body weight. The averages of blood pressures taken 4 times daily, lying and standing, were less during the administration of the diuretic in 7 patients (table 1). Supine blood pressure showed a mean decrease of 23/9 mm. Hg and standing blood pressure decreased 23/11 mm. Hg. The transverse cardiac diameter was less in all patients during chlorothiazide administration regardless of the original heart size (table 2). The decreases in transverse cardiac diameter ranged from 0.8 to 2.5 cm. and the average was 1.3 cm. Three patients were studied again after chlorothiazide had been withdrawn, and, in each, heart size was found to have returned to the control value.

Effects of Intravenous Chlorothiazide
Cardiac output, mean blood pressure, and total peripheral resistance were not affected in 2 patients 1 hour after they had received 500 mg. of chlorothiazide intravenously (table 3).

Discussion
Cardiac Output and Related Functions. The concurrence of decreased plasma volume, heart size, large decreases in cardiac output, small decreases in arterial pressure, increases of total peripheral resistance, and increased sensitivity to the depressor effect of TEAC is consistent with the view that the primary factor in determining chlorothiazide enhancement of the effects of ganglioplegic antihypertensive drugs is contraction of plasma volume, partially compensated for by increased motor tone.

The fact that TEAC had not more depressant effect on cardiac output during than it had without chlorothiazide might seem inconsistent. It is reasonable to suppose, however, that the arterial vasodilator effect of TEAC would be enhanced in the presence of increased vasomotor tone, and this assumption is supported by the fact that TEAC decreased total peripheral resistance during chlorothiazide treatment, whereas without treatment the reverse was the case. This enhanced vasodilator activity on the arterial side is apparently sufficient to offset the depressant effect on cardiac output of the venomotor paresis elicited by this ganglioplegic agent.

The observations are therefore consistent with the hypothesis that oligemia with increased vasomotor activity is the primary mechanism by which chlorothiazide potentiates the action of drugs that, like reserpine, depress, or, like the antihypertensive ganglioplegics, interfere peripherally with vasomotor outflow. This action results in a therapeutic advantage which we1 and others31 have described.

Sodium Loss as a Possible Primary Mechanism. Chlorothiazide causes a depletion of both sodium and water, and these effects are not easily separated. Sodium depletion might be antihypertensive by its effect on blood volume or, hypothetically, by withdrawing salt and water from the walls of arteries and arterioles. That the effect of chlorothiazide depends primarily on volume rather than on some action of the sodium ion is suggested by the one observation in which salt-free dextran restored cardiac output and arterial pressure during chlorothiazide-induced oligemia. As concerns the possible effects of “dehydration” of vessel walls, it should be noted that, with the exception of one patient, total peripheral resistance increased and did not decrease during treatment with chlorothiazide.

**Table 2.—Changes in Transverse Cardiac Diameter (TCD) Evoked by Chlorothiazide**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>TCD (cm.)</th>
<th>C</th>
<th>D</th>
<th>Patient no.</th>
<th>TCD (cm.)</th>
<th>C</th>
<th>D</th>
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*See footnote, table 1.
Effects of Intravenous Chlorothiazide. The fact that intravenous injection of chlorothiazide has no effects on arterial pressure, cardiac output, and peripheral resistance over the course of 1 hour demonstrates that chlorothiazide as such has no direct vasotropic hypotensive action.

Depressor Effect of Chlorothiazide Given Alone. A minority of patients respond by large decreases in arterial pressure to chlorothiazide alone, in the absence of other antihypertensive drugs. Presumably this depends on the same mechanism that determines responsiveness to strict low-sodium dietotherapy. The basic mechanism may be loss of body sodium as such or an unusual susceptibility to small decreases in blood volume. Decreased blood volume has also been observed during treatment with the rice diet. This implies that chlorothiazide can be used as a means of selecting and quantitating some of the various mechanisms of essential hypertension.

Homeostasis of Hypertension. We conceive of essential hypertension as a state resulting from the interplay of different etiologic factors whose equilibrium has been displaced in the direction of increased arterial pressure. Once established, the process tends to be self-sustaining, and the relief or removal of the primary factor may or may not relieve the hypertension, depending in part on the duration of the process. Clinical impressions with drug therapy and experience with nephrectomy in renal hypertension exemplify this generalization. A specific example was the experience in treatment of hypertension with phenoxybenzamine, an anti-adrenergic agent that blocks or damps the vasomotor component in hypertension. In some patients, notably those selected as probably having a "neurogenic" hypertension, this agent caused a prompt decrease in supine blood pressure. Over the course of several days, however, supine blood pressure rose to pretreatment levels, in spite of increasing dosage, continued adrenergic blockade, and defective vasomotor function manifested by orthostatic hypotension. This sequence demonstrates the relief of one component in hypertension, which may have been primary, and its replacement by some other pressor mechanism.

This process is also exemplified in the dog with renal hypertension, in which, with the course of time, the buffer nerves "re-set" so that this system ultimately tends to maintain, by a neurogenic mechanism, a hypertension that was primarily renal. The action of chlorothiazide in hypertension is still another case in point. Here, however, therapeutic advantage is taken of this interesting natural phenomenon. The sequence, in most patients, is that chlorothiazide decreases plasma volume and thus tends to decrease arterial pressure. The "homeostasis" of hypertension then results in increased vasomotor tone, tending to sustain pressure. At this point the administration of an agent which diminishes vasomotor tone reduces arterial pressure more effectively than it would in the absence of increased vasomotor tone.

Summary and Conclusions

Chlorothiazide, orally administered to hypertensive patients over the course of a few days, decreases plasma volume, heart size, cardiac output, and increases total peripheral resistance in most, and also sensitivity to the depressor effect of intravenously injected TEAC, without affecting the depressant effect of TEAC on cardiac output.

The data are consistent with the view that the primary mechanism by which chlorothiazide enhances responsiveness to the antihypertensive effects of drugs acting on the vasomotor system is that it causes oligemia which evokes intensification of vasomotor tone. This increases the fraction of the hypertension
which is sustained by the vasomotor system, establishing a degree of neurogenic hypertension, which is susceptible to relief by such drugs.

**SUMMARIO IN INTERLINGUA**

Chlorothiazido, quando administrate per via oral a patientes hypertensive durante un curso de plures dies, reduce le volumine del plasma, le dimensiones del corde, e le rendimento cardiac e augmenta—in le majoritate del casus—le total resistentia peripheric e le sensibilitate al effecto depressori de chloruro de tetraethylammonium, sed illo non affice le effecto depressori de chloruro de tetraethylammonium super le rendimento cardiac.

Iste datos es compatible con le concepto que le mecanismo primari per que chlorothiazido promove le responsivitate al potential anti-hypertensive de drogas que age super le systema vasomotori consiste in le facto che illo causa oligemia le qual, de su parte, evoca un intensificacion del tono vasomotori. Isto aumenta le parte del hypertension que es sustente per le systema vasomotori e estabil un grado de hypertension neurogene que es susceptible de esser alleviate per tal drogas.

**REFERENCES**


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