Relationship between Diuretic and Antihypertensive Effects of Chlorothiazide and Mercurial Diuretics

By William Hollander, M.D., Aram V. Chobanian, M.D., and Robert W. Wilkins, M.D.

Both chlorothiazide and parenteral mercurial diuretics have an antihypertensive as well as a natriuretic action. Previous observations have suggested that the antihypertensive effect is not due solely to sodium depletion. This paper expands these observations on a larger group of normotensive and hypertensive subjects and presents new studies on the effects of fluorohydrocortisone and SC-8109 (a "steroidal antagonist"), upon the sodium excretion and blood pressure of hypertensive patients during treatment with one of the diuretics.

Oral chlorothiazide has been shown by a number of workers to be effective as an antihypertensive as well as a diuretic agent. Parenteral mercurial diuretics likewise have been found to exert a hypotensive action in hypertensive subjects with or without complicating heart failure. Although the mode of action of these diuretic agents on the blood pressure has not been clearly determined, clinical and laboratory observations have suggested that the antihypertensive effects of chlorothiazide may not be due solely to sodium depletion but might result in part from some other action to the drug.

The current study presents further observations on the relationship between the saluretic and hypotensive actions of chlorothiazide and of the mercurial diuretics.

Material and Methods

Twenty ambulatory normal subjects, most of whom were medical students, were given oral chlorothiazide after a 1- to 2-week control period. They were maintained on the drug during an unrestricted dietary salt intake for 30 days at a dose of 250 mg. of chlorothiazide 3 times a day. Observations of blood pressure and weight were recorded daily.

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*Fifteen of these subjects were previously reported.

In addition, similar observations of blood pressure responses to the parenteral administration of chlorothiazide or of a mercurial diuretic were made in 15 normal and in 15 hypertensive ambulatory subjects without complicating heart failure. The hypertension was of the "essential" type except in 3 subjects who had an antecedant history suggesting either pyelonephritis or renal vascular disease. After preliminary control observations of blood pressure were obtained every 15 to 20 minutes for 3 hours, chlorothiazide was given intravenously in a dose of 1.0 Gm. over a period of 60 to 90 seconds. In the same or other individuals mercaptopurin or meralluride was injected subcutaneously or intravenously in a 2-ml. dose. After the administration of the diuretic, blood pressure was determined at intervals of 15 to 30 minutes for the first 8 hours and thereafter 8 times daily for the next 4 to 5 days. Weight was recorded before and after the administration of the diuretic. Urine was collected for the 24 hours following the injection.

Similar renal excretory and blood pressure studies were made of the effects of chlorothiazide or of a mercurial diuretic in 8 hypertensive subjects during known dietary salt intakes and following the administration of 9-α-fluorohydrocortisone or of SC-8109, a steroidal lactone. Seven of these subjects had essential hypertension and 1, C.L., had hypertension associated with occlusion of the right renal artery. Two subjects, C.L. and E.M., had been subjected to splenchnecrectomy (Smithwick) more than 1 year prior to the present study without having a marked reduction in blood pressure. All subjects had a sustained elevation of the blood pressure with grade 2 retinopathy but without complicating congestive heart failure or nitrogen retention. For at least 6 weeks prior to the study all antihypertensive drugs had been withdrawn but the dietary intake of salt was unrestricted.

*Kindly supplied by G. D. Searle and Company.
TABLE 1.—Summary of Data

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<th>Diastolic blood pressure (mm. Hg)</th>
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<td>p</td>
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One potassium balance study and 9 sodium balance studies were carried out over a period of 16 to 32 days. In order to avoid the possible effect of hospitalization and bed rest on the blood pressure, all of these subjects with the exception of C.L., H.L., and E.M. were studied while ambulatory. Daily meals, which contained a total of 9 mEq. of sodium, were prepared by the dietary department and given in the hospital. Sodium intake was adjusted by adding or withdrawing weighed amounts of sodium chloride from the basic diet. The daily potassium intake in patient H.L. was controlled at 75 mEq. by supplementing the diet each day with weighed amounts of potassium chloride. Total urine output was collected daily and analyzed for creatinine, sodium, and potassium. Serum was also analyzed for these constituents. Weight was recorded before breakfast each day and the blood pressure was measured by the auscultatory method at least 6 times throughout the day.

Serum and urinary sodium and potassium were determined by the internal standard flame photometer (lithium standard). Creatinine in the serum and urine was determined by the method of Hare. 17

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RESULTS

The effects of chlorothiazide and of parenteral mercurial diuretics on the blood pressure in normotensive and hypertensive subjects are presented statistically in table 1. The effects of these agents on blood pressure and salt excretion in hypertensive individuals are summarized in tables 2 to 5 and figures 1 to 5.

Blood Pressure Effects of Chlorothiazide

In contrast to the hypotensive action of oral chlorothiazide in arterial hypertension, 9 20 normal subjects had no significant reduction in blood pressure after 30 days on oral chlorothiazide in doses of 250 mg. 3 times daily. During the first week on the drug a weight loss of 0.5 to 2 Kg. usually occurred but without a change in blood pressure. However, by the end of the drug period there was no significant reduction in weight when compared with pre-drug values. The normotensive group likewise had no significant change in blood pressure following the intravenous injection of 1 Gm. of chlorothiazide although they did have a significant diuresis and a temporary reduction in weight.

In contrast with the normal subjects, 7 of 12 hypertensive subjects had an appreciable reduction in blood pressure varying from 20/15 to 60/30 mm. Hg following the intravenous injection of 1 Gm. of chlorothiazide. The hypotensive effect usually began within 12 to 18 hours and lasted for 24 to 48 hours. In addition to a reduction in blood pressure, chlorothiazide produced a significant diuresis and a temporary reduction in weight comparable to its effects in the normotensive controls.

Blood Pressure Effects of Parenteral Mercurial Diuretics

Parenteral mercaptomerin or meralluride had a significant hypotensive action in 8 of 15 subjects with arterial hypertension but in none of the 15 normal individuals. The reduction in blood pressure in the hypertensive group ranged from 15/10 to 60/40 mm. Hg.

The hypertensive subjects who had a reduction in blood pressure following the administration of the mercurial diuretics also had
had a similar blood pressure response to intravenous chlorothiazide. The onset of the antihypertensive effect of either meralluride or mercapto mercurial, occurred within 10 to 20 hours and lasted for 24 to 54 hours. Although the normal individuals had no significant change in blood pressure following mercurial injection, they did have an increased urinary output and a reduction in weight comparable to those observed in hypertensive individuals.

**Balance Study 1.** The effects of oral chlorothiazide on the blood pressure and sodium and potassium excretion in subject, H.L., with essential hypertension are shown in figure 1.

During a daily intake of 145 mEq. of sodium and 75 mEq. of potassium, chlorothiazide in an oral dose of 250 mg. 3 times a day produced a maximal cumulative negative balance of 170 mEq. of sodium and 136 mEq. of potassium. Accompanying the decreases in body sodium and potassium there was an appreciable reduction in blood pressure which appeared 25 hours after the start of chlorothiazide therapy. The losses in body sodium occurred during the first 2 days of treatment and were greatest on the first day of chlorothiazide administration. The losses of body potassium occurred gradually over a period of 5 days. As chlorothiazide was continued, the cumulative negative sodium balance rose toward normal, 62 to 81 mEq., but without an accompanying increase in the blood pressure.

When chlorothiazide was withdrawn and simultaneously the daily intake of sodium reduced to 9 mEq. on the twelfth metabolic day, the blood pressure did not rise but remained at the previous level of reduction. During this period the negative sodium balance previously caused by chlorothiazide persisted but the cumulative negative balance of potassium disappeared.

Following the reinstitution of chlorothiazide during the sodium restricted diet on the nineteenth metabolic day additional losses of body sodium and potassium occurred without a further reduction in blood pressure.

In general, changes in serum postassium varied in the same direction as those in the potassium balance, whereas changes in serum sodium were slight and did not necessarily accompany those in the cumulative sodium balance.
**Figs. 1 and 2.** (See legend opposite page.)
After withdrawing chlorothiazide and increasing the daily sodium intake to 145 mEq., the blood pressure increased to the pretreatment level while sodium and potassium balances returned to or above control values.

**Balance Study 2.** The effects of intravenous chlorothiazide on the blood pressure and sodium balance in subject, M.L., with essential hypertension are shown in table 2.

During a reduced sodium intake of 9 mEq. per day a cumulative negative sodium balance of 138 mEq. resulted without an appreciable change in the blood pressure. An intravenous injection of 1 Gm. of chlorothiazide on the sixth metabolic day was followed by a further sodium loss of 58 mEq. as well as a decrease in blood pressure. The reduction in blood pressure, which occurred 18 hours after the injection of chlorothiazide, persisted for 6 days along with a cumulative negative sodium balance of 149 to 196 mEq. during continued sodium restriction. After the daily sodium intake was increased to 145 mEq. on the thirteenth metabolic day, the sodium balance returned to and above control values while the blood pressure rose to pretreatment levels.

**Balance Study 3.** The effects of a parenteral mercurial diuretic on the blood pressure and sodium balance in subject, E.A., with essential hypertension are illustrated in figure 2.

After the sodium intake was restricted to 9 mEq. per day a cumulative negative sodium balance of 146 mEq. developed without a striking change in blood pressure. On the fifth metabolic day, 20 hours following the intravenous injection of mercuralluride, a marked reduction in blood pressure occurred together with an increase of 63 mEq. in the cumulative negative sodium balance. The hypotensive effect of mercuralluride like that of chlorothiazide persisted during the maintenance of sodium restriction and a negative sodium balance. However, when the daily intake of sodium was increased to 145 mEq. on the twelfth metabolic day, both the blood pressure and sodium balance returned to or above the control levels.

In repeating the same type of experiment in subject R.D. with essential hypertension (table 3) similar results were obtained. The hypotensive effect of intravenous mercaptopurin was associated with a cumulative negative sodium balance of 169 mEq. It persisted until the negative sodium balance, which was maintained by sodium restriction, reverted to and above control values following an increase of the sodium intake to 145 mEq. per day.

**Balance Study 4.** The effects of chlorothiazide and a mercurial diuretic on the blood pressure and sodium balance in a splanchnectomized subject, C.L., with renal hypertension are shown in figure 3.

During a reduced daily sodium intake of 77 mEq. the maximal reductions in blood pressure and losses of sodium occurred during the first 2 days of chlorothiazide treatment. However, the initial fall in blood pressure of 25/20 mm. Hg appeared 4 hours after the start of chlorothiazide and was associated with a net sodium loss of 48 mEq. As chlorothiazide was continued, the cumulative negative sodium balance moderated from 226 to 165 mEq. but then returned toward the greater negative values. During these changes in sodium balance the hypotensive effect of chlorothiazide was not strikingly altered.

When chlorothiazide was withdrawn while the daily sodium intake was simultaneously reduced to 9 mEq. per day on the sixteenth
Figs. 3 and 4. (See legend opposite page.)
metabolic day, the cumulative negative sodium balance continued at about the same level but the blood pressure, though still reduced, showed a slight rise.

Mercaptomerin, which was administered parenterally during the restricted sodium intake on the nineteenth and twentieth metabolic days, produced an additional net sodium loss of 63 mEq. and a further reduction in blood pressure. The hypotensive effect of mercaptomerin appeared to last for about 48 hours after the administration of the drug.

During the period of negative sodium balance there were no striking reductions in the creatinine clearance or in the serum potassium although there was a slight reduction in the serum sodium.

After all drugs were withdrawn and the daily intake of sodium was increased to 180 mEq., the blood pressure increased to the pretreatment values and the sodium balance returned to and above the control levels.

In subject E.M. with essential hypertension and previous splanchnecetomy (table 4) the onset of the hypotensive action of oral chlorothiazide during a daily sodium intake of 60 mEq. also occurred 4 hours after the administration of the drug and was associated with a net sodium loss of 52 mEq. On continuing chlorothiazide but reducing the sodium intake to 9 mEq. on the eleventh metabolic day, an additional reduction in blood pressure and increase in cumulative negative sodium balance resulted.

**Balance Study 5.** The effects of 9-α-fluorohydrocortisone on the natriuretic and hypotensive actions of chlorothiazide in subject, L.K., with essential hypertension are shown in figure 4.

During a daily intake of 163 mEq. of sodium the control blood pressure averaged 180/105 mm. Hg. After chlorothiazide was given on the seventh metabolic day the blood pressure decreased by an average of 37/15 mm. Hg and the net loss of sodium varied from 187 to 243 mEq. On the fourteenth metabolic day 9-α-fluorohydrocortisone in a daily dosage of 3 mg. was added to chlorothiazide. During the 6 days of steroid administration the cumulative negative sodium balance that followed chlorothiazide administration disappeared and sodium balance became positive as compared with control values, but the blood pressure increased only slightly and remained below control levels. Weight and serum sodium also did not change strikingly during this period whereas serum potassium decreased. After fluorohydrocortisone and chlorothiazide were both withdrawn, the blood pressure and weight rose to the control values while the net positive sodium balance, which increased initially, returned towards zero.

Similar experiments were repeated in subjects H.W. (table 5) and R.D. (fig. 5) with essential hypertension. In these subjects the hypotensive action of chlorothiazide after the addition of fluorohydrocortisone also persisted in the absence of a negative sodium balance. Although the blood pressure in subject R.D. rose as body sodium increased to and above control values following the administration of fluorohydrocortisone, it did not return to the pretreatment levels. In both of these subjects, as in subject L.K., the sodium retention following the administration of fluorohydrocortisone during chlorothiazide therapy was not accompanied by a noticeable increase in weight.

**Balance Study 6.** The effects of SC-8109, 3-(3-oxo-17 B-hydroxy-19-nor-4-androsten-17-α-yl) propionic acid lactone, on the diuretic and hypotensive actions of chlorothiazide in subject R.D. with essential hypertension are shown in figure 5.

The effects of SC-8109, a "steroidal antagonist,"18, 19 on the actions of chlorothiazide were studied because of the possibility that an increased excretion of aldosterone might account for the absence of a continued natri-

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**Fig. 3** Top. Study 4: Chlorothiazide and a mercurial diuretic in a subject with renal hypertension and splanchniecetomy.

**Fig. 4** Bottom. Study 5: 9-α-fluorohydrocortisone in a subject with essential hypertension treated with chlorothiazide.
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<tr>
<th>Balance day</th>
<th>Drugs</th>
<th>Average blood pressure (mm. Hg)</th>
<th>Weight (Kg.)</th>
<th>Sodium intake (mEq./day)</th>
<th>Urinary sodium excretion (mEq./day)</th>
<th>Daily sodium balance (mEq./day)</th>
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TABLE 4.—Oral Chlorothiazide in Splanchnicectomized Hypertensive Patient, E.M., Age 41 (Study 4)

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<th>Sodium intake (mEq./day)</th>
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<td>Chlorothiazide 750 mg./day</td>
<td>150/92</td>
<td>70.6</td>
<td>9</td>
<td>14</td>
<td>-5</td>
<td>-278</td>
</tr>
<tr>
<td>15</td>
<td>Placebo</td>
<td>172/110</td>
<td>71.5</td>
<td>145</td>
<td>3</td>
<td>+142</td>
<td>-136</td>
</tr>
<tr>
<td>16</td>
<td>Placebo</td>
<td>196/132</td>
<td>72.4</td>
<td>145</td>
<td>5</td>
<td>+140</td>
<td>+4</td>
</tr>
<tr>
<td>17</td>
<td>Placebo</td>
<td>206/135</td>
<td>72.9</td>
<td>145</td>
<td>63</td>
<td>+82</td>
<td>+86</td>
</tr>
<tr>
<td>18</td>
<td>Placebo</td>
<td>209/136</td>
<td>72.6</td>
<td>145</td>
<td>186</td>
<td>-41</td>
<td>+45</td>
</tr>
</tbody>
</table>
uretic effect of chlorothiazide and for the excess retention of sodium after the withdrawal of chlorothiazide.

On the eleventh metabolic day SC-8109 was added to chlorothiazide during a daily intake of 77 mEq. of sodium. At this time the net loss of sodium was 161 mEq, and no further reductions in body sodium and blood pressure were being produced by chlorothiazide. SC-8109 given in a daily dose of 750 mg. in combination with chlorothiazide for 4 days produced an additional loss of 181 mEq. of sodium and a decrease in blood pressure of 35/10 mm. Hg. During this period there was a slight increase in serum potassium without an appreciable change in serum sodium. After withdrawing SC-8109 and increasing the daily intake of sodium to 163 mEq. on the fifteenth metabolic day while continuing chlorothiazide, the cumulative negative sodium balance decreased and the blood pressure increased to the levels that existed before the administration of SC-8109. The remaining part of the experiment was described in study 5.

**Discussion**

Chlorothiazide or parenteral mercurial diuretics apparently exerted a hypotensive action in arterial hypertension during a daily sodium intake of 9 mEq. to 214 mEq. The reductions in blood pressure following the administration of these agents were usually associated with a cumulative negative sodium balance of 150 to 200 mEq. but occurred in splanchnecrectomized hypertensive subjects during a net sodium loss as little as 50 mEq. The continued reduction in blood pressure after withdrawing the diuretic agents and restricting sodium intake to 9 mEq. per day was also associated with a continued negative
sodium balance but not with a negative potassium balance. It seems unlikely that the continued reduction in blood pressure during this period was due to a reduced sodium intake per se, since salt restriction prior to the addition of the diuretics affected the blood pressure only slightly.

Although a reduction in body sodium may be capable of maintaining the hypotensive effect of chlorothiazide and mercurial diuretics, the balance studies in which fluorohydrocortisone was added to chlorothiazide indicate that sodium depletion from the body may not be the sole cause of the antihypertensive action of these compounds. In these studies it was found that chlorothiazide exerted a hypotensive action in the absence of a negative sodium balance. However, the increase in blood pressure...
pressure, although not to pretreatment values following the addition of fluorohydrocortisone in 2 of 3 experimental subjects, suggests that a reduction in body sodium may potentiate as well as perpetuate the antihypertensive effect of chlorothiazide. Collateral studies also indicate that chlorothiazide given alone for prolonged periods may exhibit a hypotensive effect without an accompanying decrease in body sodium or potassium.\textsuperscript{9, 12, 18} However, these as well as the present findings do not exclude local tissue shifts of electrolytes or changes in fluid volume as factors operating in the hypotensive action of chlorothiazide.

The observation that further reductions in blood pressure and body sodium were produced by the addition of SC-8109, a "steroidal antagonist,"\textsuperscript{17, 19} to the chlorothiazide treatment is consistent with the notion that an increase in aldosterone activity may occur during the administration of chlorothiazide to counteract the natriuretic and possibly some of the hypotensive effects of chlorothiazide. However, these findings do not exclude a nonspecific effect of SC-8109 on salt excretion and blood pressure. It is noteworthy that an increased aldosterone excretion has been reported to occur following the administration of mercurial diuretics.\textsuperscript{20, 21} The stimulus for an augmented aldosterone activity might be a reduced body sodium or a contracted blood volume (or both) caused initially by chlorothiazide or mercurial diuretics.

Chlorothiazide and mercurial diuretics appear to have a different antihypertensive action in patients with arterial hypertension than in normotensive subjects in whom they have no demonstrable hypotensive action. It is therefore possible that chlorothiazide and mercurials may operate similarly against some pressor mechanism. Since the antihypertensive effect of these compounds appears to be augmented and maintained by but not wholly dependent upon a reduction in total body sodium, it is conceivable that such an arterial pressor mechanism may be suppressed during the administration of chlorothiazide and mercurials with or without an accompanying change in body sodium and reactivated following the withdrawal of these agents only when body sodium is at an optimum level. Preliminary observations\textsuperscript{19} which suggested that chlorothiazide might reduce blood pressure by depressing the serum renin content, have not been confirmed.

**SUMMARY**

During a controlled sodium intake of 9 to 214 mEq. per day, chlorothiazide and parenteral mercurial diuretics produced a hypotensive effect in hypertensive patients that was associated with a negative sodium and potassium balance. The hypotensive action of these compounds, which was maintained after their withdrawal by restricting sodium intake, was also associated with a negative sodium but not a negative potassium balance. However, experiments in which fluorohydrocortisone was added to chlorothiazide indicated that chlorothiazide is capable of maintaining a lowered blood pressure in the presence of an unreduced body sodium. The natriuretic and hypotensive effects of chlorothiazide were increased by the addition of SC-8109, a steroidal lactone, to chlorothiazide. The findings that chlorothiazide and parenteral mercurial diuretics have a hypotensive action in subjects with arterial hypertension but not in normal individuals suggest that these compounds may operate similarly against some arterial pressor mechanism.

**Summario in Interlingua**

Durante un regulate ingestion diurne de 9 a 214 mEq. de natrium, chlorothiazido e mercuriales parenteral produceva un effecto hypotensive in patinetes hypertensive, associare con un balancia negative de natrium e de kalium. Le action hypotensive de iste compositos, mantenite post lor discontinuation per un restriction del ingestion de natrium, esseva etiam associate con un balancia negative de natrium sed non con un balancia negative de kalium. Tamen, experimentos in que fluorohydrocortisona esseva addite al chlorothiazido indicave que chlorothiazido es capace de mantener un redeuite tension de sanguine in
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