The Antihypertensive Actions of Benzothiadiazines

By Bertram M. Winer, M.D.

The precise mechanisms by which low-sodium diets,1 diuretics,2-4 and low-potassium diets5 are antihypertensive have not been established. Recent studies have suggested that reductions in plasma and extracellular fluid volumes play an important part in the antihypertensive action of chlorothiazide.6-8 The present studies were undertaken to elucidate the separate roles of the depletions of sodium, potassium, plasma volume, and extracellular fluid volume in the hypotensive action of benzothiadiazines. The magnitudes of the deficits, the general sites of the losses, the effects of added salt, and the effects of repletion of plasma volume were examined.

Materials and Methods

All subjects had sustained hypertension and grade two fundi (Keith-Wagener scale), without edema or renal insufficiency. Dietary sodium was not restricted.

Plasma volume was determined from two venous samples drawn without stasis 12 to 18 minutes after injection of 1131-tagged human serum albumin.9,10 The radioactivity of heparinized plasma samples and diluted injected solution was measured with a well-type scintillation counter. Twenty-four-hour exchangeable potassium and 24-hour exchangeable sodium were determined simultaneously by the differential counting technic of Robinson.11 For single determinations of exchangeable sodium a scintillation counter was used; a dip counter was used for single determinations of exchangeable potassium. Serum or plasma samples were counted to a minimum of 10,000 counts. Urine was counted to 5,000 counts. Serum and urine sodium and potassium concentrations were determined with a flame photometer. Extracellular fluid volume was measured with thiosulfate;12 four aliquots of venous blood were drawn at intervals of 10 minutes in the period 30 to 60 minutes after injection. All measurements were carried out in duplicate. Test substances were given in calibrated syringes.

All blood pressures were determined by the same technician by the auscultatory technic. During each visit in the laboratory blood pressure was measured in the sitting position at intervals of a few minutes for approximately 30 minutes. The average of the lowest two blood pressures was taken to represent the blood pressure of the day. Patients were seen at intervals of 1 to 14 days. The blood pressures of the last two visits of a period of study were averaged to represent the response of that period. In the study of the effects of re-expansion of plasma volume by intravenous infusion of Dextran, blood pressure was determined at intervals of a few minutes for 30 minutes before and 120 minutes after each infusion.

Results

Effects of Chlorothiazide

After 6 to 8 weeks of administration of chlorothiazide in daily doses of 0.75 to 1.5 Gm. (table 1) blood pressure was reduced more than 10 per cent in 16 of 20 patients. Reserpine, which had been given to 10 patients daily for months, was continued throughout this study. For the group as a whole blood pressure fell from 191/108 mm. Hg to 158/93 mm. Hg (p<.001).

Body weight decreased an average of 1.2 ± 1.8 Kg. (p<.01). The thiosulfate space, a measure of extracellular fluid,12,13 was reduced an average of 1.1 L. (p<.05). Twenty-four-hour exchangeable sodium fell 137 ± 161 mEq. (p<.01), although serum sodium concentration was unchanged. Plasma volume was reduced an average of 155 ± 271 ml. (p<.05), a change of 6 per cent. There was no consistent relationship between the changes in exchangeable sodium or plasma volume and the arterial pressure changes.

Twenty-four-hour exchangeable potassium decreased an average of 165 ± 256 mEq. (p<.05) (table 1). Serum potassium fell from 4.2 to 3.4 mEq. per liter (p<.001). Pretreatment extracellular fluid volume averaged 12 liters. There was a loss of approximately 10 mEq. of potassium from the extra-
Table 1

The Effects of Six to Eight Weeks of Chlorothiazide Therapy

<table>
<thead>
<tr>
<th>Patients</th>
<th>Before chlorothiazide</th>
<th>Blood pressure mm. Hg after chlorothiazide</th>
<th>Change</th>
<th>Weight Kg.</th>
<th>Extracellular fluid volume L.</th>
<th>Plasma volume ml.</th>
<th>24-Hour exch. sodium mEq.</th>
<th>Serum sodium mEq./L.</th>
<th>24-Hour exch. potassium mEq.</th>
<th>Serum potassium mEq./L.</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. P.</td>
<td>216/114</td>
<td>152/85</td>
<td>-64/-29</td>
<td>-0.2</td>
<td>-416</td>
<td>-72</td>
<td>+2.0</td>
<td>-229</td>
<td>-0.7</td>
<td></td>
</tr>
<tr>
<td>J. S.</td>
<td>210/102</td>
<td>164/74</td>
<td>-42/-28</td>
<td>-0.1</td>
<td>-627</td>
<td>-150</td>
<td>+0.8</td>
<td>-568</td>
<td>-0.1</td>
<td></td>
</tr>
<tr>
<td>A. K.</td>
<td>184/122</td>
<td>148/102</td>
<td>-36/-20</td>
<td>-2.6</td>
<td>-317</td>
<td>-15</td>
<td>+2.3</td>
<td>-511</td>
<td>-0.5</td>
<td></td>
</tr>
<tr>
<td>I. F.</td>
<td>185/104</td>
<td>150/96</td>
<td>-32/-8</td>
<td>-1.3</td>
<td>-663</td>
<td>-139</td>
<td>+5.7</td>
<td>-421</td>
<td>-0.9</td>
<td></td>
</tr>
<tr>
<td>M. K.</td>
<td>170/108</td>
<td>146/92</td>
<td>-24/-16</td>
<td>-0.7</td>
<td>-115</td>
<td>-52</td>
<td>-3.5</td>
<td>-511</td>
<td>-1.0</td>
<td></td>
</tr>
<tr>
<td>M. M.</td>
<td>193/93</td>
<td>170/82</td>
<td>-23/-13</td>
<td>-0.8</td>
<td>-15</td>
<td>-50</td>
<td>-1.8</td>
<td>-42</td>
<td>-1.4</td>
<td></td>
</tr>
<tr>
<td>L. R.</td>
<td>167/115</td>
<td>147/102</td>
<td>-20/-13</td>
<td>-0.4</td>
<td>-170</td>
<td>-127</td>
<td>+4.9</td>
<td>+3</td>
<td>-0.5</td>
<td></td>
</tr>
<tr>
<td>F. Z.</td>
<td>209/106</td>
<td>193/97</td>
<td>-16/-9</td>
<td>+0.3</td>
<td>-113</td>
<td>-3.8</td>
<td>-134</td>
<td>-3</td>
<td>-0.3</td>
<td></td>
</tr>
<tr>
<td>L. P.</td>
<td>184/112</td>
<td>171/104</td>
<td>-13/-8</td>
<td>0.0</td>
<td>-291</td>
<td>+65</td>
<td>0.0</td>
<td>-360</td>
<td>-1.1</td>
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</tr>
<tr>
<td>L. A.</td>
<td>194/127</td>
<td>173/127</td>
<td>-10/-3</td>
<td>+0.5</td>
<td>+144</td>
<td>-130</td>
<td>-1.1</td>
<td>-40</td>
<td>-0.1</td>
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</tr>
<tr>
<td>C. J.</td>
<td>172/100</td>
<td>119/74</td>
<td>-53/-26</td>
<td>-1.0</td>
<td>+83</td>
<td>-33</td>
<td>+2.8</td>
<td>-499</td>
<td>-1.1</td>
<td></td>
</tr>
<tr>
<td>M. L.</td>
<td>176/109</td>
<td>125/82</td>
<td>-51/-27</td>
<td>-3.6</td>
<td>+125</td>
<td>-211</td>
<td>-2.5</td>
<td>-19</td>
<td>-0.5</td>
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</tr>
<tr>
<td>L. C.</td>
<td>201/103</td>
<td>146/87</td>
<td>-55/-16</td>
<td>-0.7</td>
<td>-89</td>
<td>-1.9</td>
<td>+378</td>
<td>-0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F. B.</td>
<td>212/102</td>
<td>161/89</td>
<td>-51/-13</td>
<td>-0.3</td>
<td>+92</td>
<td>-51</td>
<td>+0.9</td>
<td>-0.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. L.</td>
<td>200/120</td>
<td>166/98</td>
<td>-54/-22</td>
<td>-1.6</td>
<td>+44</td>
<td>-199</td>
<td>-3.6</td>
<td>-93</td>
<td>-0.2</td>
<td></td>
</tr>
<tr>
<td>S. G.</td>
<td>176/99</td>
<td>140/85</td>
<td>-36/-14</td>
<td>+0.6</td>
<td>+227</td>
<td>-42</td>
<td>-0.9</td>
<td>+107</td>
<td>-0.6</td>
<td></td>
</tr>
<tr>
<td>C. M.</td>
<td>178/90</td>
<td>152/74</td>
<td>-26/-16</td>
<td>-0.8</td>
<td>-131</td>
<td>-149</td>
<td>-0.5</td>
<td>-15</td>
<td>-0.9</td>
<td></td>
</tr>
<tr>
<td>H. A.</td>
<td>148/90</td>
<td>121/81</td>
<td>-27/-9</td>
<td>-0.6</td>
<td>+83</td>
<td>-544</td>
<td>-2.7</td>
<td>-8</td>
<td>-0.8</td>
<td></td>
</tr>
<tr>
<td>G. M.</td>
<td>102/98</td>
<td>165/87</td>
<td>-27/-11</td>
<td>-2.0</td>
<td>-274</td>
<td>-180</td>
<td>-4.3</td>
<td>-203</td>
<td>-1.6</td>
<td></td>
</tr>
<tr>
<td>W. R.</td>
<td>244/146</td>
<td>240/144</td>
<td>-4/-2</td>
<td>+0.8</td>
<td>-560</td>
<td>-562</td>
<td>-2.3</td>
<td>-0.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean: 101/108 158/93  
Standard deviation: ±15.8/±8.0  
*p* <.001/ <.001  

1. Winer.
ANTIHYPERTENSIVE ACTIONS OF BENZOTHIADIAZINES

Table 2
Effects of the Addition of Twenty Grams of Sodium Chloride Daily during Continuous Administration of Hydrochlorothiazide or Chlorothiazide

<table>
<thead>
<tr>
<th>Patient</th>
<th>Blood pressure mm. Hg</th>
<th>Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before thiazide</td>
<td>After thiazide</td>
</tr>
<tr>
<td>H. F.</td>
<td>203/112</td>
<td>191/102*</td>
</tr>
<tr>
<td>I. F.</td>
<td>198/104</td>
<td>179/94*</td>
</tr>
<tr>
<td>M. F.</td>
<td>220/113</td>
<td>201/104*</td>
</tr>
<tr>
<td>M. K.</td>
<td>173/105</td>
<td>150/97*</td>
</tr>
<tr>
<td>S. G.</td>
<td>205/115</td>
<td>176/103*</td>
</tr>
<tr>
<td>P. G.</td>
<td>209/118</td>
<td>196/108*</td>
</tr>
<tr>
<td>I. R.</td>
<td>184/111</td>
<td>154/103*</td>
</tr>
<tr>
<td>J. A.</td>
<td>186/103</td>
<td>154/92*</td>
</tr>
<tr>
<td>R. R.</td>
<td>196/101</td>
<td>169/92*</td>
</tr>
<tr>
<td>P. G.</td>
<td>179/112</td>
<td>146/94†</td>
</tr>
<tr>
<td>Menn†</td>
<td>197/109</td>
<td>174/99</td>
</tr>
<tr>
<td>Menn change‡</td>
<td>-23/-10</td>
<td>+19/46†</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>7/1</td>
<td>10/5</td>
</tr>
</tbody>
</table>

*p < .001/

✝Calculated from data in daily doses of 150 mg.

✝Observations in patient P. G. during chlorothiazide were not included in calculations of the mean values.

Effects of Two Dosage Levels of Added Salt

After 4 weeks of administration of hydrochlorothiazide in daily doses of 150 mg., blood pressure and body weight were reduced in each of nine hypertensive subjects (table 2). The addition of 20 Gm. of sodium chloride daily for 2 weeks was attended by return of blood pressure and body weight approximately to control levels. Average blood pressure fell from 197/109 to 174/99 mm. Hg during the diuretic (p < .001) and rose to 193/105 mm. Hg during the addition of the salt load (p < .001). Body weight, which had decreased an average of 1.6 ± .99 Kg. (p < .01) during hydrochlorothiazide, increased an average of 1.2 ± .5 Kg. (p < .01) when the salt was added. The average 24-hour urinary excretion of sodium was 267 mEq. greater (p < .001) on the last day of the salt load than it had been before the addition of salt.

Twenty-four-hour exchangeable potassium decreased during hydrochlorothiazide administration in each of five subjects studied and remained low after the addition of salt (table 2). The large salt load further reduced body potassium, the average 24-hour exchangeable potassium falling an additional 128 ± 96 mEq. (p < .05).

In one subject 20 Gm. of sodium chloride were given daily for a week in the third month of administration of chlorothiazide. Blood pressure and body weight returned approximately to control levels (table 2).

The effects of the addition of 6 to 12 Gm. of salt daily for 1 to 12 weeks were examined in 10 hypertensive subjects during continued chlorothiazide therapy (table 3). These patients had taken chlorothiazide in doses of 0.75 to 1.5 Gm. daily for 1.5 to 7 months (average 4.0 months). The blood pressure, which had fallen from an average of 184/100 to 147/86 mm. Hg (p < .001) during administration of the diuretic, remained at the lower levels (average 148/84 mm. Hg) during this salt load. Body weight decreased 1 Kg. (p < .01) during chlorothiazide and in the group as a whole did not rise significantly when 6 to 12 Gm. of salt were added daily.
Three patients, however, had a gain in weight of approximately 1 Kg.

Effects of Repletion of Plasma Volume

Plasma volume was re-expanded by intravenous administration of 500 ml. of 6 per cent Dextran in 5 per cent glucose in water in 10 hypertensive subjects who had been treated with chlorothiazide or hydrochlorothiazide daily for 2 weeks to 9 months (average 2.5 months) (table 4). Each patient was given 500 ml. of 6 per cent Dextran in 5 per cent glucose in water intravenously at a rate of approximately 20 ml. per minute. Within 90 minutes plasma volume increased an average of 395 ± 231 ml. (p<.001). The hematocrit value fell an average of 4.2 ± 1.5 per cent (p<.001). Plasma volume was slightly overexpanded (mean + 161 ± 135 ml., p<.05) when compared in six cases with control values, an observation corroborated by the inverse changes in hematocrit level (table 4).

Systolic blood pressure rose but did not reach control levels when plasma volume was re-expanded (table 4). Diastolic pressure was unaffected. Blood pressure fell from an average of 191/111 to 159/91 mm. Hg during the diuretic (p<.001). After Dextran the blood pressure averaged 168/93 mm. Hg. The increase in systolic pressure was statistically significant (p<.01).

Discussion

Body sodium, potassium, and plasma volume are not increased in uncomplicated hypertensive disease. Nonetheless, the reduction of blood pressure associated with the administration of chlorothiazide in non-edematous hypertensive subjects coincides with the increased urinary excretion of sodium, potassium, and water. The saluresis is essentially complete in 48 hours. Extra-cellular fluid volume and plasma volume decrease promptly.

The source of the excreted sodium appears to be the extracellular fluid. The decreases in body weight, extracellular fluid volume, and 24-hour exchangeable sodium in the present studies after 6 to 8 weeks of chlorothiazide therapy are consistent with the loss of approximately a liter of isotonic extracellular fluid. These observations, in agreement with others, do not suggest a loss of sodium or water from the intracellular space.

A fundamental relationship between the salt loss and the antihypertensive action of benzothiadiazines is indicated by the return of body weight and blood pressure approximately.
to control levels after the addition of 20 Gm. of sodium chloride daily during hydrochlorothiazide or chlorothiazide therapy. The efficiency of chlorothiazide as a saluretic agent was demonstrated by the observation that the addition of 8 Gm. of sodium chloride daily did not usually restore body weight to control levels, and in this study did not oppose the antihypertensive effect. Salt loads of 11 to 20 Gm. daily were found by others 20 to reverse the effects of chlorothiazide.

The deficit of potassium in the absence of a sodium deficit does not have a role in the antihypertensive action of benzothiadiazines. When the blood pressure was returned to the original hypertensive levels by the addition of 20 Gm. of salt daily, 24-hour exchangeable potassium remained low. Indeed, potassium was further depleted by the salt load ($p < .05$), a finding consistent with increased exchange of sodium and potassium at the distal tubule in response to an increased filtered load of sodium. Potassium was lost from both extracellular and intracellular fluid.

Plasma volume is reduced as much as 30 per cent in the first week of administration of chlorothiazide. 20 The degree of oligemia lessens in the course of several months. The reduction in plasma volume averaged 6 per cent after 2 months of continuous diuretic therapy in the present study ($p < .05$) and was insignificant after 6 months in another study. 6 Right heart pressure and cardiac output were reduced and peripheral vascular resistance increased in the first few weeks in several studies 21-23 but not in the study of Aleksandrow et al. 19 After 1 month of chlorothiazide therapy, peripheral vascular resistance was decreased. 24

Oligemia and reduced cardiac output will exaggerate the effects of other drugs or pathophysiologic states influencing venous return, cardiac output, or vascular capacity. The hypotensive effects of ganglion-blocking agents, sympathectomy, and nitrates are increased by benzothiadiazines. 24, 25-28 Dustan et al. have suggested that oligemia enhances neurogenic vasomotor tone, fostering increased responsiveness to ganglioplegic agents. 22

Wilson and Freis 6 found that during treatment with chlorothiazide, restoration of plasma volume by Dextran in saline or by Dextran in glucose in water returned blood pressure to pretreatment levels. In the present studies,
although plasma volume was slightly over-expanded by Dextran, systolic blood pressure rose but did not reach control levels, and diastolic pressure remained at the lower levels induced by the diuretic.

Substantiating the latter results are studies of the pressor responses to norepinephrine and the depressor responses to trimethapam and erythrol tetranitrate before and after continuous hydrochlorothiazide therapy, after intravenous infusion of Dextran and after the addition of 20 Gm. of salt daily: plasma volume repletion by Dextran diminished the effects of the diuretic on systolic responses to the vasoactive substances but had little effect on the diastolic responses; the addition of salt reverted these responses to control levels.27, 28 Physiologic studies have demonstrated that changes in circulating volume or cardiac output exert a greater effect on systolic than on diastolic pressure.29

Although reduced plasma volume flow favors a fall in blood pressure, the baroreceptor reflexes oppose this effect. Chlorothiazide does not lower the blood pressure in normotensive patients. Hypertensive patients may have defective compensatory mechanisms, but another action of sodium depletion may exaggerate the effects of oligemia. The accumulated observations indicate that oligemia plays a role early in the antihypertensive action of benzothiadiazines but that salt loss must involve another mechanism by which peripheral vascular resistance is reduced.

Arteriolar muscular contractility may be impaired by altered relationships between extracellular and intracellular sodium. In vitro, changes in sodium gradient across cell membranes affect contractility.30 Mendlovitz et al. observed a decrease in digital vascular reactivity to l-norepinephrine in hypertensive subjects during chlorothiazide therapy.31

In conflict with the thesis that sodium loss affects the sodium gradient and interferes with arteriolar contractility are the following observations. 1. The loss of sodium after benzothiadiazines appears to be isotonic and extracellular. 2. Although the absolute blood pressures during infusions of norepinephrine 32–35 or hypertension36 are lower during administration of a diuretic than in a control period, the relative increments are equal or greater, 28, 36 suggesting that the ability of the arteriolar bed to respond to pressor substances is not reduced by sodium loss.

A reduction in tissue pressure or a decrease in arteriolar wall thickness may contribute to the antihypertensive effect of chlorothiazide. Tobian and Binion suggested that arteriolar walls are "water-logged" in hypertensive states.37 Body sodium has, however, been found within normal limits in uncomplicated hypertension.14–17 Extracellular fluid volume was elevated in some studies of experimental and human hypertension,38–41 but not in others.14, 42, 43

Salt depletion may impair the function of a humoral or neurogenic pressor system. Hollander et al. were unable to demonstrate a decrease in renin during diuretic therapy.4 Further studies of possible interrelationships between sodium depletion and pressor systems are indicated. The incomplete blocking of the antihypertensive effects of benzothiadiazines by restoration of plasma volume, the studies suggesting maintenance of the ability of the arteriolar bed to respond to pressor substances, and the decrease in peripheral vascular resistance observed after 4 weeks of therapy would be explained by such a mechanism.

A direct effect of benzothiadiazines on the central nervous system or the peripheral vessels appears unlikely in view of the fact that salt repletion returns both basal blood pressures and the responses to vasoactive substances to control values.

Summary and Conclusions

Blood pressure, body weight, extracellular fluid and plasma volumes, 24-hour exchangeable sodium and potassium, and serum potassium were reduced after 6 to 8 weeks of administration of chlorothiazide in 20 nonedematous hypertensive subjects. The loss of weight, water, and sodium approximated the loss of a liter of isotonic extracellular fluid.

The addition of 20 Gm. of salt daily to
hydrochlorothiazide therapy in nine patients and chlorothiazide therapy in one patient returned body weight and blood pressure to pretreatment levels, but further lowered 24-hour exchangeable potassium. The addition of 8 Gm. of salt daily usually failed to restore body weight to control levels and did not oppose the antihypertensive effects of chlorothiazide.

Expansion of plasma volume by Dextran to levels slightly above pretreatment values was associated with (1) a rise in systolic blood pressure but not to control levels and (2) no significant change in diastolic levels in 10 patients during administration of benzo-thiadiazine.

The antihypertensive effects of benzo-thiadiazines are due to sodium depletion and are not related to potassium loss. At least two mechanisms of antihypertensive action must be involved, one related to the effects of oligemia, and another possibly to an impairment of the function of a humoral or neurogenic pressor system.

Acknowledgment

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References


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BERTRAM M. WINER

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