Effects of Chlorothiazide on Systemic Hemodynamics in Essential Hypertension

By Herman Villarreal, M.D., José Emilio Exaire, M.D., Andrés Revollo, M.D., and Jorge Soní, M.D.

Chlorothiazide lowers arterial blood pressure in hypertensive patients under either acute or long-term administration. The antihypertensive action of this substance is complex. In some instances, the drop in blood pressure is due to a reduction in cardiac output produced by contraction of the intravascular space resulting from its diuretic effect whereas in others it is due to a decrease in peripheral vascular resistance.

The purpose of this investigation was to make a comparative study in the same patient of the effect of the acute and long-term administration of chlorothiazide upon systemic hemodynamics.

Material and Methods

Nineteen observations were made in 12 patients with essential hypertension. The effect of a single intravenous dose of 500 mg. was studied in 10 instances and that of prolonged oral administration of 500 mg. every 6 hours in nine.

The patients were at rest on low-salt diet and placebo. Basal and casual blood pressure readings were taken daily. As soon as these were stabilized, mean arterial blood pressure and cardiac output under basal conditions were determined. These studies were repeated from 50 to 110 minutes following the intravenous application of chlorothiazide (average 70 minutes). Administration of the drug was continued by mouth until pressure readings were stabilized. This took place within 8 to 31 days (average 15 days) after which the same studies were repeated.

Mean blood pressure was taken directly at the left humeral artery with an electronic oscilloscope (strain gage).

Cardiac output was determined by the Fick principle in five of the acute studies and by the T-1824 dilution method in the other five. The latter procedure was employed in all cases of long-term administration. Cardiac index was calculated per square meter of body surface.

Total peripheral resistance was calculated as a function of mean arterial blood pressure and cardiac output.

Results

Mean arterial blood pressure, cardiac index, and total peripheral resistance under acute and prolonged administration of chlorothiazide are shown in table 1. Table 2 presents the statistical analyses of these results.

Mean arterial blood pressure decreased with the acute administration of chlorothiazide in all patients. The fall varied from 6 to 27 mm. Hg, with an average of 13 mm. Hg, or 10 per cent (fig. 1). Reduction of mean arterial blood pressure was greater with long-term administration, varying from 10 to 47 mm. Hg, an average of 27 mm. Hg, or 21 per cent (fig. 2).

In all patients given chlorothiazide intravenously, cardiac index was reduced. The decrease varied from 0.175 to 0.789 L./min./M.², an average of 0.470 L./min./M.², or 18 per cent (fig. 1). However, with long-term use of chlorothiazide, cardiac index rose in all cases between 0.055 and 0.359 L./min./M.², except in one case (C.G.). The average increment was 0.130 L./min./M.², or 4 per cent (fig. 2).

Total peripheral resistance rose with intravenous administration of chlorothiazide in all cases. The increment varied between 15 and 525 dynes/cm.⁵/sec., an average of 206 dynes/cm.⁵/sec., or 7 per cent (fig. 1). With long-term administration, on the other hand, there was a marked drop in all patients of 186 to 1,355 dynes/cm.⁵/sec., an average of 641 dynes/cm.⁵/sec., or 26 per cent (fig. 2).

Discussion

Both acute and long-term administration of chlorothiazide brought about a significant decrease in mean arterial blood pressure (p <
Changes in Mean Arterial Blood Pressure, Cardiac Index, and Total Peripheral Resistance Observed under Acute and Long-Term Administration of Chlorothiazide in 12 Patients with Essential Hypertension

<table>
<thead>
<tr>
<th>Patient</th>
<th>Mean arterial blood pressure (mm. Hg)</th>
<th>Cardiac index (L./min./M.²)</th>
<th>Total peripheral resistance (dynes/cm.²/sec.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.V.</td>
<td>180</td>
<td>170</td>
<td>—</td>
</tr>
<tr>
<td>L.B.</td>
<td>107</td>
<td>93</td>
<td>—</td>
</tr>
<tr>
<td>S.P.</td>
<td>130</td>
<td>103</td>
<td>—</td>
</tr>
<tr>
<td>F.T.</td>
<td>160</td>
<td>148</td>
<td>120</td>
</tr>
<tr>
<td>I.S.</td>
<td>144</td>
<td>130</td>
<td>97</td>
</tr>
<tr>
<td>V.G.</td>
<td>168</td>
<td>158</td>
<td>140</td>
</tr>
<tr>
<td>A.G.</td>
<td>130</td>
<td>120</td>
<td>98</td>
</tr>
<tr>
<td>S.M.</td>
<td>115</td>
<td>109</td>
<td>102</td>
</tr>
<tr>
<td>E.O.</td>
<td>127</td>
<td>110</td>
<td>100</td>
</tr>
<tr>
<td>V.P.</td>
<td>137</td>
<td>131</td>
<td>103</td>
</tr>
<tr>
<td>J.C.</td>
<td>114</td>
<td>—</td>
<td>104</td>
</tr>
<tr>
<td>C.G.</td>
<td>112</td>
<td>—</td>
<td>101</td>
</tr>
</tbody>
</table>

Statistical Analysis of Results

<table>
<thead>
<tr>
<th></th>
<th>Control*</th>
<th>Acute*</th>
<th>Change</th>
<th>Control†</th>
<th>Long-term†</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial blood pressure, mm. Hg</td>
<td>140</td>
<td>127</td>
<td>-13</td>
<td>134</td>
<td>107</td>
<td>-27</td>
</tr>
<tr>
<td></td>
<td>±23</td>
<td>±25</td>
<td>*p&lt;0.001</td>
<td>±20</td>
<td>±14</td>
<td>*p&lt;0.001</td>
</tr>
<tr>
<td>Cardiac index, L./min./M.²</td>
<td>2.758</td>
<td>2.288</td>
<td>-0.470</td>
<td>2.619</td>
<td>2.749</td>
<td>+0.130</td>
</tr>
<tr>
<td></td>
<td>±0.584</td>
<td>±0.470</td>
<td>*p&lt;0.001</td>
<td>±0.652</td>
<td>±0.607</td>
<td>*p&gt;0.05</td>
</tr>
<tr>
<td>Total peripheral resistance, dynes/cm.²/sec.</td>
<td>2617</td>
<td>2823</td>
<td>+206</td>
<td>2550</td>
<td>1909</td>
<td>-641</td>
</tr>
<tr>
<td></td>
<td>±805</td>
<td>±876</td>
<td>*p&lt;0.01</td>
<td>±775</td>
<td>±514</td>
<td>*p&lt;0.01</td>
</tr>
</tbody>
</table>

*Mean and standard deviation in 10 observations,
†Mean and standard deviation in nine observations.

Changes in cardiac index, on the other hand, followed a different pattern. While acute intravenous administration of the drug produced significant reduction (*p < 0.001), long-term use showed no significant change (*p > 0.05).

Under the acute effect of the drug, decrease in mean arterial blood pressure was related to decrease in cardiac output. It has been thought that drop in cardiac output is produced by the contraction of the intravascular space through the saluretic effect of chlorothiazide. Nevertheless, it is hard to accept that the saluretic effect of the drug should have been sufficient after only 70 minutes of action to be responsible for the fall in cardiac output. It is possible that chlorothiazide acts in some way upon the peripheral circulation producing a decrease of venous return. Supporting this hypothesis is the fact that when the legs of patients under the effect of chlorothiazide are raised, venous return increases and cardiac output reverts to its previous value.

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Total peripheral resistance increased significantly ($p < 0.01$) with the intravenous administration of chlorothiazide. However, the drop in cardiac index was greater than the increase in peripheral resistance, which accounts for the fall in mean arterial blood pressure.

In the case of long-term use of chlorothiazide, reduction in mean arterial blood pressure was produced by the decrease in peripheral resistance ($p < 0.01$). Although the mode of action by which the thiazides lower peripheral resistance is unknown, it is believed that it is related to modifications in the reactivity of the arterioles resulting from changes in the concentration of water and sodium in their walls.\[^{8,7}\]

In cases of prolonged use cardiac output not only became normal, but went above the control values. However, the changes were not significant ($p > 0.05$).

Comparative study of the acute and long-term effect of chlorothiazide shows that cardiac output decreases markedly on acute administration of the drug and returns to its previous values during long-term use. The fall in cardiac output was observed 70 minutes after administration of the drug. This can only be explained by direct action upon venous return. On the other hand, peripheral resistance, which rises slightly with acute administration, decreases markedly with long-term use.

Summary

Nineteen observations were made in 12 patients with early essential hypertension. The comparative effects upon mean arterial blood pressure, cardiac index, and total peripheral resistance of the acute and long-term administration of chlorothiazide were studied.

With acute administration of the drug, a 10 per cent drop in mean arterial blood pressure, a decrease of 18 per cent in cardiac index, and an increase of 7 per cent in peripheral resistance were observed.

With long-term administration, a decrease of 21 per cent in mean arterial blood pressure, an increase of 4 per cent in cardiac index, and a drop of 26 per cent in peripheral resistance were found.

The conclusion is drawn that reduction of mean arterial blood pressure with acute administration of chlorothiazide is due to decrease in cardiac output, whereas with long-term use it is due to reduction in total peripheral resistance.

References

3. Courand, A., Ranges, H. A., and Riley, R. L.: Comparison of results of the normal ballisto-
On Permanent Patency of the Mouth of the Aorta, or Inadequacy of the Aortic Valves

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... When the aortic valves are fully adequate to their function of perfectly closing the mouth of the aorta, and thus preventing any regurgitation of blood, the aorta and its branches are kept fully distended, the blood is at each contraction of the ventricle propelled forward en masse, and there is no trembling, or vibratory motion of the sides of the aorta, carotids, and subclavians, and, as in the flexible tube when fully distended, no sound is emitted. But when the valves, becoming inadequate to their office, permit some of the blood contained in the ascending aorta, carotids, and subclavians, to return into the left ventricle after each contraction, then the aorta and these trunks become ... partially flaccid; and at the next contraction of the ventricle, the blood propelled into them is sent along as a rushing current, which throws the sides of these arteries into vibrations, and these vibrations give to the ear bruit de soufflet, and to the finger fremissement. These two signs may be traced to a varying distance from the mouth of the aorta, and always along the carotids, and to the outer third of the subclavians, and sometimes in the brachial arteries, as far as the bend of the arms, the distance to which they are heard being determined by the limit to which the current-like motion of the blood producing them is extended. In those cases in which the deficiency of the valves is considerable, allowing a full stream of blood to rush back into the ventricle, there is heard in the ascending aorta a double bruit; the first accompanying the diastole of the artery, the second immediately succeeding; and, in listening to the two sounds constituting this double bruit de soufflet, the impression made distinctly on the ear is, that the first sound is from a rushing of blood up the aorta, the second from a rushing of it back into the ventricle. It is impossible for those who have not heard this double bruit to conceive the distinctness with which the impression described is made on the ear. A patient in one instance heard this double sound distinctly in his own person, and referred it to its cause, a rushing of blood from and to the heart. The bruit de soufflet and fremissement are not perceived in the arteries of the lower extremities, when the patient is in a sitting or standing posture. The pressure of the blood in the abdominal aorta is sufficient in these postures to keep the vessels arising from it fully distended; and thus no vibratory motion of their parietes being permitted, there is no bellows sound, nor fremissement or rushing thrill.
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