Cardiovascular Effects of Acebutolol and Hydrochlorothiazide in Essential Hypertension

RICHARD I. OGLIVIE, M.D., F.R.C.P.(C), and JOHN H. NADEAU, M.D., F.R.C.P.(C)

SUMMARY During a double-blind crossover study of hydrochlorothiazide (HCT) and acebutolol (ACB), 11 patients 45 to 69 years old with essential hypertension underwent studies of forearm blood flow (FBF), arterial resistance (FAR), and venous compliance (FVC) using mercury-in-Silastic plethysmography. Placebo periods of 12 weeks were followed by a variable period of incremental doses of either active drug and a final 12-week period at fixed dosage averaging 168 mg/day of HCT (range 100 to 200 mg) or 678 mg/day of ACB (range 400 to 800 mg). Supine diastolic pressures decreased (x ± SEM) from 98 ± 2 to 91 ± 3 mm Hg on HCT (p < 0.05) and from 99 ± 2 to 90 ± 4 mm Hg on ACB (p < 0.05). FAR decreased from 62.4 ± 10.6 to 47.1 ± 6.4 units after HCT (p < 0.05) and from 61.4 ± 10.7 to 53.7 ± 10.0 units after ACB (p < 0.05), whereas FVC increased 24.2% ± 10.9% after HCT (p < 0.05) and 29.1% ± 10.4% after ACB (p < 0.01). Although changes in FAR and FVC were similar after each drug, they were not correlated. Body weight was unaltered by either drug, yet HCT reduced pulse pressure, increased peripheral renin activity, and reduced serum potassium, whereas ACB did not alter these variables. Heart rates increased from 81 to 87 beats/min after HCT but decreased from 82 to 71 beats/min (p < 0.05) after ACB, resulting in a greater decrease in double product (heart rate x systolic pressure) after ACB. Although a similar proportion of patients had diastolic pressures < 90 mm Hg on HCT (6/11) as on ACB (7/11) and peripheral vascular effects were comparable, the central cardiovascular effects of these drugs were quite different. (Hypertension 4: 320-324, 1982)

Key Words - forearm blood flow • vascular resistance • venous compliance • tension-time index

The mechanism underlying the hypotensive effect of long-term treatment of essential hypertension with either diuretics or beta-blockers is unclear. Diuretics may initially reduce circulating volume and cardiac output, but with continued use, measurements of plasma volume and cardiac output usually return to normal whereas total peripheral resistance is diminished. Beta-blockers initially cause a reduction in heart rate, stroke volume, and cardiac output, with increased total peripheral resistance and unchanged blood pressure. After long-term treatment, blood pressure and peripheral resistance are decreased. We undertook to study the effects of diuretic and beta-blockade therapy on the central and peripheral circulation during a double-blind crossover comparative study of hydrochlorothiazide (HCT) vs acebutolol (ACB), a cardioselective beta adrenoceptor blocking agent.

Methods

During a double-blind crossover study of 19 patients with essential hypertension using ACB and HCT,11 patients volunteered for additional studies of forearm circulation. Placebo periods of 12 weeks were followed by a variable period of incremental dose titration of either active drug and a final 12-week period at final dosage of the active drug. A 12-week washout period with placebo followed with the second titration and maintenance dose period with the alternate active drug. Placebo tablets, and ACB 200 mg and HCT 50 mg tablets were identical in appearance.

The patients were seen every 2 weeks while on placebo and every 3 weeks while on active drug. Blood pressures were recorded, after subjects had 15-minutes of rest in the supine position, using a mercury sphygmomanometer and taking the disappearance of
VASCULAR EFFECTS OF ACEBUTOLOL AND HYDROCHLOROTHIAZIDE/Ogilvie and Nadeau

Korotkoff's sounds as the diastolic pressure. Upright blood pressures were recorded after patients had 2 minutes in the erect position. The tension-time index was calculated from the product of the systolic blood pressure and heart rate in each of the erect and supine positions. At the end of the placebo and active drug treatment periods, body weight, serum electrolytes, and stimulated plasma renin activity were measured. The plasma for renin activity was taken 4 hours after oral furosemide 40 mg and upright activity, as reported previously. A normal response in our laboratory is 3 to 13 ng/ml-hr.

Studies of forearm circulation were carried out at the end of each placebo period and at the end of each maintenance period of active drug therapy. Patients reported to the laboratory approximately 4 hours after ingesting their medications. Studies were carried out with the patient resting in a recumbent position with the arm supported at the midthoracic level in a controlled environment of 20°C and 40% relative humidity; mercury-in-Silastic plethysmography was used as reported previously. Forearm venous pressure was measured via a catheter inserted into a deep vein in the antecubital fossa in a retrograde direction and attached to a Clarke (427) pressure transducer (fig. 1). Systemic arterial pressure was measured by sphygmomanometry in the opposite arm. Mean arterial pressure was calculated from the sum of the diastolic pressure plus one-third of the pulse pressure (systolic-diastolic pressure). Forearm blood flow (FBF) was measured by intermittent rapid inflation of a venous occlusion cuff mounted on the upper arm to a pressure of 40 mm Hg while the hand was excluded from the circulation by a wrist cuff inflated to 240 mm Hg. Forearm venous compliance (FVC) was calculated from the relationship between changes in forearm volume and venous pressure (AV/AP) during gradual occlusion of venous flow. The venous occlusion cuff was inflated at a steady rate of less than 0.25 mm Hg/sec with continuous recording of forearm venous volume and pressure until a change of 30 mm Hg above starting pressure had been achieved.

Forearm arterial resistance (FAR) was calculated in arbitrary units by dividing the forearm blood flow into the pressure gradient determined from the difference between mean arterial and venous pressures. The paired t test was used to assess the significance of changes.

Results

Eight men and three women volunteered for the study; they had an average age of 57 years (range, 45 to 69 years). Seven of the 11 patients were randomly allocated to receive HCT as the first active drug. The mean daily dose of HCT was 168 mg (range, 100 to 200 mg), and the mean daily dose of ACB was 473 mg (range, 400 to 800 mg). Nine of the 11 patients received more than 100 mg of HCT daily, and eight of the 11 received more than 400 mg of ACB daily. These drug doses resulted in equivalent reductions in diastolic blood pressure. Therapy with HCT was associated with a decrease in supine diastolic pressure from 98 ± 2 mm Hg on placebo to 91 ± 3 mm Hg, whereas therapy with ACB was associated with a decrease from 99 ± 2 mm Hg on placebo to 90 ± 4 mm Hg. Six of the 11 patients had supine diastolic pressures < 90 mm Hg with HCT whereas seven of the 11 had diastolic pressures below this value with ACB.

Changes observed in the upright position after active therapy are given in table 1. Neither HCT nor ACB consistently altered body weight. Heart rates tended to increase after HCT and to decrease after ACB. Although both drugs decreased systolic pressure and tension-time index (systolic pressure X heart rate), the decrease in the double product was more marked with ACB due to a lower heart rate. Reductions in systolic and pulse pressures were more marked with HCT. Peripheral renin activity was increased and serum potassium reduced after HCT but were unchanged after ACB.

The results of the plethysmographic determination of forearm blood flow, arterial resistance and venous compliance are given in table 2. Both HCT and ACB therapy resulted in small increases in forearm blood flow, marked decreases in arterial resistance, and modest increases in venous compliance. Plots of the changes in forearm volume against incremental increases in forearm venous pressure reveal similar volume-pressure curves for HCT (fig. 2) and ACB (fig. 3).

The mean percent changes in FAR and FVC were similar after the two treatments. Vascular resistance was reduced 18.1% ± 9.1% after HCT and 13.6% ± 7.2% after ACB, whereas venous compliance was increased 24.2% ± 10.9% after HCT and 29.1% ± 10.4% after ACB. A scattergram presentation of changes in resistance and compliance (fig. 4) indicate a lack of correlation between the two after treatment with either HCT or ACB.
TABLE 1. Changes Observed in the Upright Position after Therapy with Hydrochlorothiazide (HCT) or Acebutolol (ACB)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>HCT</th>
<th>Placebo</th>
<th>ACB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>80.6 ± 6.1</td>
<td>78.8 ± 5.6</td>
<td>81.0 ± 5.9</td>
<td>80.3 ± 6.3</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>81 ± 3</td>
<td>87 ± 5</td>
<td>82 ± 4</td>
<td>71 ± 3*</td>
</tr>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td>159 ± 6</td>
<td>135 ± 6†</td>
<td>158 ± 5</td>
<td>143 ± 9*</td>
</tr>
<tr>
<td>Tension-time index</td>
<td>129 ± 7</td>
<td>117 ± 7*</td>
<td>130 ± 8</td>
<td>103 ± 9†</td>
</tr>
<tr>
<td>Pulse pressure (mm Hg)</td>
<td>55.7 ± 4.3</td>
<td>41.6 ± 4.6†</td>
<td>52.9 ± 3.1</td>
<td>50.5 ± 4.6</td>
</tr>
<tr>
<td>PRA (ng/ml/hr⁻¹)</td>
<td>3.3 ± 0.4</td>
<td>11.1 ± 2.1†</td>
<td>3.4 ± 0.8</td>
<td>2.6 ± 0.6</td>
</tr>
<tr>
<td>Serum potassium (mEq/liter)</td>
<td>4.2 ± 0.1</td>
<td>3.4 ± 0.1†</td>
<td>4.1 ± 0.1</td>
<td>4.2 ± 0.1</td>
</tr>
</tbody>
</table>

Tension-time index = systolic pressure × heart rate/100.
PRA = peripheral renin activity after 4 hours in the upright position and furosemide 40 mg p.o.
* p < 0.05.
† p < 0.01.

TABLE 2. Changes in Forearm Circulation in the Supine Position after Therapy with Hydrochlorothiazide (HCT) or Acebutolol (ACB)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>HCT</th>
<th>Placebo</th>
<th>ACB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>127 ± 3</td>
<td>106 ± 3†</td>
<td>125 ± 3</td>
<td>109 ± 2†</td>
</tr>
<tr>
<td>Forearm blood flow (ml/min/100 ml volume)</td>
<td>2.52 ± 0.34</td>
<td>2.72 ± 0.41</td>
<td>2.48 ± 0.32</td>
<td>2.72 ± 0.46</td>
</tr>
<tr>
<td>Forearm arterial resistance (units)</td>
<td>62.4 ± 10.6</td>
<td>47.1 ± 6.4*</td>
<td>61.4 ± 10.7</td>
<td>53.7 ± 10.0*</td>
</tr>
<tr>
<td>Forearm venous compliance (ml/mm Hg/100 ml volume)</td>
<td>0.066 ± 0.006</td>
<td>0.080 ± 0.009*</td>
<td>0.073 ± 0.006</td>
<td>0.086 ± 0.009†</td>
</tr>
</tbody>
</table>

* p < 0.05.
† p < 0.01.

Figure 2. Forearm venous pressure-volume curves at the end of placebo and at the end of more than 12 weeks of therapy with hydrochlorothiazide obtained during gradual increase in venous pressure following inflation of the occluding cuff.

Figure 3. Forearm venous pressure-volume curves at the end of placebo and at the end of over 12 weeks of therapy with acebutolol obtained during gradual increase in venous pressure following inflation of the occluding cuff.
FIGURE 4. Relation between changes in forearm arterial resistance and venous compliance after more than 12 weeks of therapy with hydrochlorothiazide (HCT) or acebutolol during a crossover study of 11 patients. The dotted line indicates the relationship that would exist if there was perfect correlation between reductions in forearm arterial resistance and increases in forearm venous compliance.

Discussion

Both hydrochlorothiazide (HCT) and acebutolol (ACB) effectively lowered blood pressure in this crossover comparison of intermediate term therapy (> 12 weeks) in patients with essential hypertension. The reduced blood pressure was associated with comparable effects on peripheral vascular resistance and venous compliance, yet the central cardiovascular effects of the two drugs were quite different. Heart rates were increased after HCT and reduced after ACB. The reduction in tension-time index was greater after ACB than after HCT. Although body weight was unaltered by either drug, HCT treatment reduced pulse pressure, increased peripheral renin activity, and reduced serum potassium, whereas ACB did not alter these variables.

In contrast, both HCT and ACB reduced forearm vascular resistance. It is well accepted that increased peripheral vascular resistance is a primary factor in the maintenance of high blood pressure in established hypertension. However, it is not clear whether treatment with HCT or ACB reduced forearm vascular resistance in our patients as a primary mechanism or secondarily as a consequence of lowering blood pressure by some other mechanism, but it seems unlikely that reductions in blood pressure could be sustained without modifying vascular resistance toward normal.

Therapy with HCT could cause arteriolar smooth muscle relaxation by a direct action similar to that caused by the nondiuretic benzothiadiazine, diazoxide. It could also alter vascular smooth muscle responsiveness to neurohumoral stimulation. In animals, it has been demonstrated that HCT therapy increased sympathetic nerve traffic but reduced response of vascular smooth muscle to these impulses. In contrast, it has been postulated that administration of beta blockers reduces sympathetic nerve traffic due to a central mechanism. Because ACB treatment was associated with a decreased peripheral vascular resistance in our patients, it would appear that its peripheral effects on β₂ receptors of blood vessels was minimal so that any reflex increase in alpha activity would be balanced by intact beta activity. This may be the reason that we observed a reduction in vascular resistance after beta blockade therapy. On the other hand, the cardioselectivity of acebutolol in humans has been questioned.

Although this study does not reveal the mechanism, we presume acebutolol reduced vascular resistance because of a longer term of therapy (> 12 weeks) whereas acute or short term beta blockade often results in reduced or unchanged vascular resistance. Intermediate term therapy (8 weeks) with pindolol has been observed to reduce both the calculated systemic and forearm vascular resistance at rest and during exercise in 10 patients with essential hypertension.

The effect of chronic beta blockade might be on CNS or baroreceptor function but this study does not provide the answer as to the mechanism involved.

Both HCT and ACB therapy resulted in increased forearm venous compliance. It has been clearly demonstrated that patients with essential hypertension have reduced peripheral venous compliance and capacitance which could augment venous return and cardiac output. Increased peripheral venous compliance and capacitance following HCT or ACB treatment would reduce the central blood volume and limit changes in cardiac output. Chronic therapy with propranolol has been associated with a decreased measured central blood volume and central venous pressure and a limited increase in cardiac output in response to a saline volume load largely due to a decrease in stroke volume. A similar experiment has not been carried out with HCT or ACB. We have previously demonstrated that HCT therapy was associated with a dose-related decrement in venoconstrictor response to deep breaths or Valsalva maneuvers. Other investigators have documented an increased forearm venous distensibility in a few patients after HCT therapy. The present study confirms these previous limited findings. Additionally, it demonstrates that forearm venous compliance is also increased after chronic beta adrenoceptor blockade with ACB. A similar finding was reported in 10 patients with essential hypertension treated with pindolol for 8 weeks.

In summary, the present study demonstrates that reduction of blood pressure following HCT or ACB therapy was associated with a reduction in peripheral vascular resistance and an increase in peripheral venous compliance but does not provide further information on the responsible mechanisms. Since changes in vascular resistance and venous compliance were ap-
parently not correlated after either drug therapy, it is possible that more than one mechanism was operative. The different effects of these two agents on heart rate, tension-time index, and peripheral renin activity do not help us resolve the mechanism underlying their similar effects on the peripheral circulation.

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