Antihypertensive and metabolic effects of a combination of hydrochlorothiazide and amiloride

W. P. LEARY, A. J. REYES

Summary
A combination of hydrochlorothiazide 50 mg and amiloride 5 mg (HTZ + AMI) was administered twice daily for 12 weeks to 18 hypertensive patients, as a monotherapy. There was a statistically and clinically significant decrease in the mean blood pressure level throughout the treatment period.

Significant steady or random changes in blood variables included decreases in chloride, magnesium and bilirubin levels and increases in sodium, calcium, phosphorus, creatinine, triglycerides, total protein, albumin, alkaline phosphatase and SGPT levels. Blood urea nitrogen values changed biphasically. Most of these statistically significant metabolic changes had no clinical relevance.

The dosage problem with HTZ + AMI is discussed.

Diuretics are the drugs of first choice in the treatment of hypertension. A combination of hydrochlorothiazide 50 mg and the potassium-sparing diuretic amiloride 5 mg (HTZ + AMI) has been demonstrated to be an effective antihypertensive medication when used as monotherapy. However, published observations on the metabolic effects of this drug combination do not provide comprehensive cover of biochemical variables in blood and are not consistent with each other.

The principal objective of this study was to evaluate the metabolic effects of HTZ + AMI administered to hypertensive patients at its highest recommended dose of 2 tablets per day.

Patients and methods

Patients
Eighteen ambulatory male patients aged 21 - 65 years consented to participate in the trial after they had been fully informed about its objectives and implications. Patients had mild-to-moderately severe hypertension with supine diastolic blood pressure readings between 90 and 120 mmHg. Fourteen were Blacks and 4 were Whites.

Patients who fell within one or more of the following categories were not included in the trial: secondary or renal hypertension, congestive cardiac failure, a history of severe cerebrovascular or hepatic impairment, impaired renal function (creatinine > 2 mg/dl), hyperkalaemia (> 6.0 mEq/l) or hypokalaemia (< 3.5 mEq/l), clinical evidence or history of gout, abnormal pretreatment laboratory tests (except high blood glucose which was not an exclusion criterion), or retinopathy more severe than slight irregularity or narrowing of vessels. Patients taking cardiac glycosides or psychotropic drugs were also excluded.

Measurements
Arterial pressures were measured in the working arm by the standard indirect technique, using the first appearance and final disappearance of Korotkoff's sounds to define systolic and diastolic pressures, respectively. The mean arterial blood pressure was defined as the diastolic pressure plus one-third of the pulse pressure. Patients rested supine for 10 minutes and stood upright for 3 minutes before measurement of supine and erect pressures, which were each measured three times, the average values being recorded. All blood pressure measurements were done between 08h00 and 09h30. The sphygmonanometer and stethoscope used for blood pressure measurements were the same throughout the trial. Clinical evaluations were carried out by the same observer physician throughout the trial.

The following variables were measured in blood or serum samples by standard laboratory techniques in 14 patients: chloride, sodium, potassium, calcium, phosphorus, magnesium, osmolality, blood urea nitrogen, creatinine, uric acid, glucose, cholesterol, triglycerides, total protein, albumin, bilirubin, alkaline phosphatase, γ-glutamyltransferase, SGOT and SGPT.

Procedure
All diuretic and/or antihypertensive medication being taken by the patients was discontinued and 1 placebo capsule was prescribed twice daily for 4 weeks. HTZ + AMI was then substituted for 12 weeks, and thereafter placebo was prescribed as in the run-in period for 4 more weeks.

Diet was not restricted, and contained approximately 2 g sodium per day. Complete clinical evaluations were carried out every 4 weeks. Laboratory analyses were done at the beginning of the trial, at the end of the run-in placebo period (referred to as week 0 hereafter) and at the end of the 4th, 8th and 12th weeks of active treatment.

Statistics
Results are expressed as mean values ± standard errors of the means (SEM). Values during treatment and after treatment were contrasted with pretreatment (week 0) values. Variance homogeneities were tested through the F ratio. When variances were homogeneous, a paired t test was used to compare mean
Effects of HTZ + AMI on arterial blood pressure and heart rate

HTZ + AMI decreased mean blood pressure significantly compared with control values (Fig. 1). These changes were of clinical significance but 4 weeks after treatment was discontinued mean blood pressure did not differ significantly from control (week 0) levels (Fig. 1).

A significant increase (P<0.05) in heart rate was observed at the end of week 8. However, it had no clinical importance, ranging from 77.8 ± 2.6/min in week 0 to 83.1 ± 2.0/min in week 12.

Effects of HTZ + AMI on serum electrolytes

The results are shown in Table I. Serum chloride decreased significantly throughout the treatment period, its lowest level being found at the end of week 4; it recovered, but was still below control levels thereafter. Serum sodium had increased significantly by the end of week 8. Serum potassium did not change significantly during treatment. Serum calcium was significantly increased at the end of week 8. Serum phosphorus was significantly increased at the end of weeks 4 and 8 and returned to control levels at the end of week 12. Serum magnesium was significantly below control level at the end of week 12.

Effects of HTZ + AMI on biochemical blood variables other than electrolytes

The results are shown in Table II. Plasma osmolality did not change significantly during HTZ + AMI treatment. Blood urea nitrogen increased significantly by the end of week 4, decreasing to control values at the end of week 8 and finally decreasing significantly compared with pretreatment levels at the end of week 12. Serum creatinine was found to be significantly increased at the end of weeks 4 and 8 and returned to normal values at the end of week 12. It followed a decreasing trend throughout treatment that paralleled that of blood urea nitrogen. Serum uric acid did not change significantly during HTZ + AMI treatment.

Blood glucose did not change significantly during HTZ + AMI treatment. However, as 4 patients were diabetics under dietary treatment, two different biological populations as regards blood glucose should be considered; one group, consisting of 10 patients, was a population of non-diabetics whose blood glucose values did not change significantly during treatment (Table II). The other population consisted of 4 diabetics who were not fully compensated and whose management was not changed during HTZ + AMI treatment; blood glucose did not change significantly in this group either during treatment with HTZ + AMI.

Plasma cholesterol did not change significantly during HTZ + AMI treatment and serum triglycerides were found to be increased compared with week 0 only at the end of week 8 of treatment.

Total plasma protein was significantly increased at the ends of week 8 and week 12 of treatment, whereas plasma albumin was significantly increased throughout treatment. Serum bilirubin was found to be significantly decreased at the end of weeks 4 and 12. Serum alkaline phosphatase was significantly increased at the end of weeks 8 and 12 of HTZ + AMI treatment. However, as 4 patients were diabetics under dietary treatment, two different biological populations as regards \( \gamma \)-glutamyltransferase and SGOT did not change significantly during treatment. SGPT increased significantly at the end of week 12.

Significances of differences with respect to pretreatment means:

- \( P<0.05 \)
- \( P<0.02 \)
- \( P<0.01 \)
- \( \beta P<0.001 \)

### Table I. Serum Electrolyte Concentrations (Mean ± SEM) in 14 Hypertensive Patients Before and During Treatment with a Combination of HTZ + AMI

<table>
<thead>
<tr>
<th>Electrolyte</th>
<th>Pretreatment (last on placebo)</th>
<th>At the end of treatment week:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>4 &lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Chloride (mEq/l)</td>
<td>102.6 ± 0.8</td>
<td>97.7 ± 0.85</td>
</tr>
<tr>
<td>Sodium (mEq/l)</td>
<td>145.1 ± 0.6</td>
<td>146.5 ± 0.9</td>
</tr>
<tr>
<td>Potassium (mEq/l)</td>
<td>4.11 ± 0.06</td>
<td>4.21 ± 0.01</td>
</tr>
<tr>
<td>Calcium (mmol/l)</td>
<td>2.44 ± 0.04</td>
<td>2.53 ± 0.03</td>
</tr>
<tr>
<td>Phosphorus (mmol/l)</td>
<td>1.12 ± 0.03</td>
<td>1.33 ± 0.05&lt;sup&gt;12&lt;/sup&gt;</td>
</tr>
<tr>
<td>Magnesium (mmol/l)</td>
<td>0.85 ± 0.02</td>
<td>0.86 ± 0.02</td>
</tr>
</tbody>
</table>

Significances of differences with respect to pretreatment means:

- \( P<0.05 \)
- \( P<0.02 \)
- \( P<0.01 \)
- \( \beta P<0.001 \)
No change occurred in biochemical variables in individual patients that could indicate a toxic effect of the drug combination. HTZ + AMI was well tolerated and no clinical signs of side-effects were observed.

**Discussion**

**Effects of HTZ + AMI on serum electrolytes**

The significant decrease found in serum chloride values is a well-recognized effect of thiazide diuretics. The trend whereby serum chloride levels returned toward reference levels as treatment progressed indicates that homeostatic adjustments take place during prolonged diuretic treatment.1

The transient significant increase in serum sodium found at the end of week 8 of treatment was irrelevant in clinical terms. Serum potassium values did not change significantly during HTZ + AMI treatment, since what actually matters, both physiologically and clinically, is the intracellular potassium level.1 Normal serum potassium levels do not necessarily reflect normal intracellular levels since potassium has to be actively pumped into the cells in order to keep its high intracellular concentration; the activity of the potassium pump is critically determined by the intracellular level of magnesium.1 Diuretics increase renal magnesium excretion and may provoke magnesium depletion, which is usually observed as a decrease in serum magnesium occurring rather late in treatment,1 as was the case in this trial, in which serum magnesium was found to be significantly decreased only at the end of week 12. A thorough assessment of these complicated interactions and of the effects of HTZ + AMI in this respect requires more detailed long-term studies. However, serum potassium is one of the determinants of intracellular potassium1 and during hydrochlorothiazide treatment it is preferable to keep it within the normal range by using a potassium-sparing diuretic like amiloride, since potassium supplements induce a higher percentage of side-effects.7

The transient increase in serum calcium levels that occurred at the end of week 8 is indicative of an increase in calcium reabsorption in the proximal tubule which is provoked by hydrochlorothiazide and may be related to the proximal tubular increase in sodium and water reabsorption that occurs during treatment with thiazide diuretics; these changes might in turn be secondary to plasma volume contraction provoked by these diuretics.7 A regulatory effect of the increased calcium reabsorption elicited by hydrochlorothiazide could be an increased secretion of thyrocalcitonin, whose augmented activity could explain the significant increases in serum phosphorus levels that were observed at the end of weeks 4 and 8 of HTZ + AMI treatment. Thyrocalcitonin is known to decrease renal handling of calcium induced by these drugs.8 The renal loss of magnesium provoked by diuretics therefore does not appear to be related to the altered renal handling of calcium induced by these drugs.

**Effects of HTZ + AMI on biochemical blood variables other than electrolytes**

The significant increase in blood urea nitrogen and serum creatinine levels at the end of week 4 of HTZ + AMI treatment tended to return towards control values, surpassing them in the case of blood urea nitrogen. The mechanisms whereby these changes occur are similar to those discussed for calcium.

Serum uric acid and blood glucose are usually increased during treatment with a thiazide diuretic. However, neither of them was found to be significantly increased during HTZ + AMI treatment. The reason serum uric acid levels did not rise significantly is far from clear, although the intimate renal handling of uric acid is obscure, despite extensive

**TABLE II. HAEMATOLOGICAL VARIABLES (MEAN ± SEM) OTHER THAN SERUM ELECTROLYTES IN 14 HYPERTENSIVE PATIENTS BEFORE AND DURING TREATMENT WITH HTZ + AMI TWICE DAILY**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pretreatment (last on placebo)</th>
<th>At the end of treatment week:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Osmolality (mOsm/kg)</td>
<td>281.3 ± 1.8</td>
<td>283.9 ± 3.9</td>
</tr>
<tr>
<td>BUN (mmol/l)</td>
<td>4.05 ± 0.33</td>
<td>5.48 ± 0.42</td>
</tr>
<tr>
<td>Creatinine (mmol/l)</td>
<td>101.4 ± 3.7</td>
<td>120.5 ± 5.7</td>
</tr>
<tr>
<td>Uric acid (mmol/l)</td>
<td>0.31 ± 0.02</td>
<td>0.32 ± 0.02</td>
</tr>
<tr>
<td>Glucose (N = 14) (mg/dl)</td>
<td>120.7 ± 16.2</td>
<td>140.5 ± 20.5</td>
</tr>
<tr>
<td>Glucose (N = 10) (mg/dl)</td>
<td>95.5 ± 5.0</td>
<td>103.3 ± 6.2</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>4.69 ± 0.27</td>
<td>4.70 ± 0.30</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>2.07 ± 0.25</td>
<td>2.31 ± 0.24</td>
</tr>
<tr>
<td>Total protein (g/l)</td>
<td>76.6 ± 1.4</td>
<td>77.0 ± 1.3</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>43.5 ± 1.2</td>
<td>46.3 ± 0.6</td>
</tr>
<tr>
<td>Bilirubin (µmol/l)</td>
<td>9.69 ± 1.23</td>
<td>5.27 ± 0.98</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/l)</td>
<td>120.1 ± 7.9</td>
<td>135.0 ± 10.6</td>
</tr>
<tr>
<td>γ-glutaryltransferase (U/l)</td>
<td>51.4 ± 10.2</td>
<td>59.8 ± 11.5</td>
</tr>
<tr>
<td>SGOT (U/l)</td>
<td>21.1 ± 1.9</td>
<td>23.4 ± 2.2</td>
</tr>
<tr>
<td>SGPT (U/l)</td>
<td>14.1 ± 1.3</td>
<td>16.2 ± 1.9</td>
</tr>
</tbody>
</table>

Significances of differences with respect to pretreatment means:

1P<0.05
2P<0.02
3P<0.01
4P<0.001
5Data from 13 patients.
6Data from 12 patients.
research. The reason for the lack of any significant change in blood glucose during HTZ + AMI treatment is also uncertain. Amiloride does not increase serum uric acid and blood glucose per se, whereas hydrochlorothiazide does, and the lack of change during HTZ + AMI treatment could be particularly important when diabetes-prone populations are being treated.

Plasma cholesterol levels did not change significantly and triglycerides were found to be significantly increased only at the end of week 8 of HTZ + AMI treatment. Serum lipids are increased by thiazide and loop diuretics,10-14 because of an augmented lipolysis in adipose tissue and a subsequent augmented synthesis of mainly very-low-density lipoprotein in the liver. Whether the increase in lipolysis is elicited by an increase in the sympathetic drive, secondary to plasma volume contraction provoked by diuretics, or is due to the fact that diuretics inhibit phosphodiesterase activity, thus increasing intracellular levels of cyclic adenosine monophosphate, is not known. For a better description of the effects of HTZ + AMI on serum lipids, it would be necessary to study the different lipoprotein fractions. The ultimate significance of the serum lipid-raising effect of diuretics on overall cardiovascular prognosis is not known.

The significant increases found in total serum protein and albumin levels during HTZ + AMI treatment could be due to haemoconcentration secondary to the volume depletion provoked by diuretics.

The significant increases in serum alkaline phosphatase levels during HTZ + AMI treatment are not obviously due to intrahepatic obstruction as assessed by the lack of significant increases in plasma cholesterol and albumin; they cannot be explained on the basis of the changes in calcium either. Nevertheless, these increases in serum alkaline phosphatase were of no clinical relevance.

Serum γ-glutaryltransferase and SGOT levels did not change significantly during treatment and SGPT only increased significantly at the end of week 12 of treatment; this change was of no clinical importance, thus indicating that HTZ + AMI is a safe medication from the point of view of the liver.

**HTZ + AMI dosage in hypertension**

As the principal aim of this study was to evaluate the metabolic safety of HTZ + AMI, high doses were used. However, it is now known that effective antihypertensive diuretics exert their maximal hypotensive effect at a dose lower than their standard diuretic dose. Therefore, even though HTZ + AMI was found to be safe at the dosage studied, it would be reasonable to prescribe a dose of 1/2 - 1 tablet per day in the initial treatment of hypertension. Lower doses may spare magnesium and potassium and, in addition, cause less long-term derangement of metabolism.

**REFERENCES**


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**Fenbufen as a single daily dose in the treatment of rheumatoid arthritis**

**L. SOLOMON, K. FINEGAN**

**Summary**

Fenbufen (3(4-biphenyl-carbonyl) propionic acid) (Cinopal; Lederle) was administered as a single daily dose of 1 000 mg for 4 weeks to 20 patients with rheumatoid arthritis. At 2 weeks, and again at the end of the trial, patients were assessed for duration of morning stiffness, number of painful and/or swollen joints, grip strength, walking time, and subjective response to treatment. Four patients failed to complete the trial, 2 because of inability to control symptoms and 2 because of severe rash attributed to the drug. The remaining 16 patients showed some improvement in most of the recorded parameters, with statistically significant reduction of morning stiffness and walking time.

Apart from a maculopapular rash, which occurred in 4 patients and cleared up on stopping the fenbufen, side-effects were minimal. No patient complained of dyspepsia or epigastric pain.

In previous studies fenbufen (3(4-biphenyl-carbonyl) propionic acid) (Cinopal; Lederle) has been shown to be an effective analgesic and anti-inflammatory agent in the treatment of rheumatoid arthritis (RA) and osteo-arthritis, with a therapeutic