The Blood Pressure Response to Antihypertensive Treatment With Lisinopril or Bendrofluazide Is Related to the Calcium and Magnesium Contents in Skeletal Muscle

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To evaluate the association between skeletal muscle mineral balance and effect of antihypertensive treatment, 37 patients with essential hypertension, randomly treated with either lisinopril or bendrofluazide, were investigated with skeletal muscle biopsies before and after 6 months of treatment. The ratio between calcium and magnesium concentrations in skeletal muscle prior to treatment predicted the blood pressure response during active treatment ($r = -0.38, P < .02$). During treatment the change in blood pressure was related to the change in muscle Ca/Mg ratio ($r = 0.35, P < .05$), especially in the patients treated with lisinopril. Thus, an association between the calcium and magnesium balance in skeletal muscle and the blood pressure response to antihypertensive treatment was found in the present study. Am J Hypertens 1996;9:273-276

KEY WORDS: Bendrofluazide, lisinopril, hypertension, muscle minerals, calcium, magnesium.

Subjects and Methods

A random sample of 37 of the 50 patients with essential hypertension entered a trial that has previously been described in detail. Sixteen patients, mean age 57, of whom four were female, were treated with lisinopril; and 21 patients, mean age 59, of whom six were female, received bendrofluazide medication. After a period of placebo treatment of 4 to 6 weeks, in which the supine diastolic blood pressure (DBP) was 95 to 115 mm Hg at least twice, the patients were randomly assigned to treatment with lisinopril 10 or 20 mg once daily or bendrofluazide 2.5 or 5 mg once daily for 24 weeks, the dose depending on the blood pressure control. Blood pressure was measured in duplicate with a sphygmomanometer after 5 min in the supine position and after 2 min in the standing position.

Skeletal muscle biopsies were performed in the right femoral vastus lateralis muscle. The muscle biopsy specimen was dissected free from visible fat and...
TABLE 1. MINERAL CHARACTERISTICS OF THE HYPERTENSIVE PATIENTS (N = 37) DURING THE INITIAL PLACEBO RUN-IN (O). ADJUSTED MEANS (± SD) FOR SODIUM, POTASSIUM, CALCIUM, AND MAGNESIUM CONCENTRATIONS (mmol/kg DRY MATTER), AND CA/MG AND NA/K RATIOS IN SKELETAL MUSCLE TISSUE, AND THE CHANGES DURING 6 MONTHS OF TREATMENT WITH LISINOPRIL (L) (N = 16) OR BENDROFLUAZIDE (B) (N = 21).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Treatment</th>
<th>Placebo (O)</th>
<th>Effect of Treatment %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>L</td>
<td>146 (55)</td>
<td>+8% NS</td>
</tr>
<tr>
<td></td>
<td>R</td>
<td>147 (100)</td>
<td>+16% NS</td>
</tr>
<tr>
<td>K</td>
<td>L</td>
<td>382 (155)</td>
<td>-2% NS</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>400 (110)</td>
<td>-7% NS</td>
</tr>
<tr>
<td>Ca</td>
<td>L</td>
<td>4.5 (2.3)</td>
<td>-1% NS</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>4.6 (2.2)</td>
<td>+16% NS</td>
</tr>
<tr>
<td>Mg</td>
<td>L</td>
<td>34 (14)</td>
<td>-4% NS</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>40 (8)</td>
<td>-13% NS</td>
</tr>
<tr>
<td>Ca/Mg ratio</td>
<td>L</td>
<td>0.14 (0.06)</td>
<td>0% NS</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>0.16 (0.04)</td>
<td>+13% NS</td>
</tr>
<tr>
<td>Na/K ratio</td>
<td>L</td>
<td>0.43 (0.19)</td>
<td>-2% NS</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>0.42 (0.18)</td>
<td>+17% NS</td>
</tr>
</tbody>
</table>

nificantly correlated with each other (r = 0.64, P < .0001) at baseline, as were the observed changes in these ratios (r = 0.70, P < .0001) (Figure 1). No significant correlations were found between individual ion concentrations in the serum and the corresponding ion concentration in the muscle, either at the basal level or during active treatment.

In the lisinopril-treated patients, the Ca/Mg ratio in skeletal muscle at baseline predicted the changes in SBP both in the supine and standing positions (r = -0.48 to -0.57, P < .03 to .07). The changes in SBP in both positions, and in DBP in the supine position, were correlated to the change in muscle Ca/Mg ratio during the treatment period (r = 0.50 to 0.61, P < .01 to .05). In the bendrofluazide-treated patients these correlations were not significant, but as no statistically significant differences were found between the two drug effects, the two treatment groups were also analyzed together (Figure 2). There were no significant correlations between changes in blood pressure and changes in muscle Na/K ratio.

DISCUSSION

The present study showed that the Ca/Mg ratio in skeletal muscle is associated with blood pressure regulation, as a relative increase in the magnesium content in skeletal muscle, compared with the calcium content, was associated with a fairly pronounced decrease in blood pressure during treatment. Furthermore, the Ca/Mg ratio in skeletal muscle was found to be a predictor for the blood pressure response to antihypertensive treatment.

In previous studies, Lindner et al noted a correlation between the calcium concentration in erythrocytes and blood pressure, and observed a reduced calcium concentration in erythrocytes from patients in whom the blood pressure was reduced during treatment with antihypertensive drugs such as lisino-
FIGURE 2. The correlation between the change in the Ca/Mg ratio in skeletal muscle tissue (ΔCa/Mg) and the change in diastolic blood pressure in the supine position (ΔDBP sup) in hypertensives treated with lisinopril (L) or bendrofluazide (B) and in these patients combined (B + L).

pril, hydrochlorothiazide, and nifedipine. Similar findings have been described by Erne et al. Paolisso et al treated elderly nonobese hypertensive subjects with magnesium and nifedipine infusion and noted a correlation between the changes in the Ca/Mg ratio in erythrocytes and the decline in blood pressure. Recently, Resnick et al reported lower intracellular free magnesium levels in skeletal muscle of subjects with essential hypertension compared with normotensives. Calcium is a primary regulator of contraction both in skeletal and in vascular smooth muscle. Magnesium has been shown to have relaxing effects on different vascular preparations, exerted by blocking of calcium entry into cells. Thus, assuming that parallel mineral changes occur in skeletal and vascular smooth muscle, a reduced Ca/Mg ratio would theoretically lead to vasodilatation. Why the association between the changes in calcium and magnesium concentrations in skeletal muscle and the anti-hypertensive response to lisinopril was more pronounced than that for the thiazide is not known, but the ability of diuretic therapy to concomitantly lower blood pressure and deplete magnesium may help to explain the poor correlation between changes in blood pressure with changes in Ca/Mg ratios. This is emphasized by the work of Dyckner and Wester, who showed that magnesium supplementation given to diuretic-treated hypertensives both elevated muscle magnesium content and further lowered blood pressure.

It has previously been found that an adequate intracellular magnesium concentration is necessary for the intracellular potassium balance, as the Na⁺-K⁺ pump transporting potassium into the intracellular space is conducted by magnesium-dependent phosphorylation, and as magnesium inhibits the K⁺ efflux via potassium channels. The close relationship observed in the present study confirms these observations.

In summary, an association between the calcium and magnesium balance in skeletal muscle and the blood pressure response to antihypertensive treatment was found in the present study, suggesting that ion balance is involved in blood pressure regulation.

REFERENCES

