Sodium Restriction in Hypertensive Patients Treated With a Converting Enzyme Inhibitor and a Thiazide

Donald R.J. Singer, Nirmala D. Markandu, A. Louise Sugden, Michelle A. Miller, and Graham A. MacGregor

When the function of the renin system is inhibited, blood pressure becomes more dependent on changes in sodium and water balance. Diuretics alone and sodium restriction alone are additive to converting enzyme inhibitor therapy. However, it is not known if these two ways of reducing sodium balance are additive in the presence of established converting enzyme inhibition. We therefore performed a double-blind crossover study of the effects of moderate sodium restriction in 21 patients with essential hypertension who were already being treated with the combination of a converting enzyme inhibitor and a diuretic. After 1 month of captopril (50 mg twice daily) and hydrochlorothiazide (25 mg once daily) therapy, with their usual sodium intake, average supine blood pressure was 147/96±5/3 (SEM) mm Hg 2 hours after treatment. Patients then reduced their sodium intake to around 80-100 mmol/day for the remainder of the study. After 2 weeks of sodium restriction, they entered a double-blind, randomized, crossover study of Slow Sodium (100 mmol sodium/day) compared with Slow Sodium placebo, while continuing sodium restriction and the above treatment. During the double-blind study, after 1 month of treatment with captopril (50 mg twice daily), hydrochlorothiazide (25 mg once daily), and Slow Sodium placebo, supine blood pressure 2 hours after treatment was 138/88±4/2 mm Hg (24-hour urinary sodium 104±11 mmol). After 1 month of captopril (50 mg twice daily), hydrochlorothiazide (25 mg once daily), and Slow Sodium tablets, supine blood pressure 2 hours after treatment was 147/91±5/2 mm Hg (p<0.05; 24-hour urinary sodium 195±14 mmol). Mean supine blood pressure fell with moderate sodium restriction by 5±2% at 2 hours and 7±2% at 12 hours after treatment with captopril and hydrochlorothiazide. The decrease in blood pressure was significantly correlated with the reduction in sodium intake. These results clearly demonstrate that a moderate reduction in salt intake does have a further blood pressure-lowering effect in patients already treated with the combination of captopril and a diuretic. This moderate change in diet provides an effective and well-tolerated way to improve blood pressure control in patients treated with the combination of an angiotensin converting enzyme inhibitor and a diuretic. (Hypertension 1991;17:798-803)

Moderate restriction of salt intake is known to lower blood pressure in many patients with essential hypertension. However, the extent of the fall in blood pressure in an individual patient appears to depend inversely on the reactive rise in renin release, and thereby angiotensin II, as sodium is lost from the body. Similar findings have also been reported with diuretics. However, once the function of the renin system is inhibited, such as occurs with converting enzyme inhibitors, both salt restriction alone and diuretics alone cause a further fall in blood pressure that is dependent on the amount of sodium loss. However, not all hypertension is controlled with the combination of a converting enzyme inhibitor and a diuretic.

We therefore examined in a double-blind, placebo-controlled, crossover study the effect of moderate sodium restriction on blood pressure in patients who were already being treated with the combination of a converting enzyme inhibitor and a thiazide diuretic.

Methods

Patients who were included in the study had uncomplicated essential hypertension. They were ac-
customed to having their blood pressure measured under standardized conditions and had been referred by local general practitioners to the Blood Pressure Unit. All subjects had been treated with captopril (50 mg twice daily) and hydrochlorothiazide (25 mg once daily) for at least 1 month before entry to the study to which they gave written, informed consent. Patients with ischemic heart disease, cerebrovascular disease, renal or hepatic impairment, and diabetes mellitus, or who were being given any additional treatment were excluded from the study. Twenty-one patients (13 men, eight women; 15 white, six black) with an average supine blood pressure, 12 hours after treatment, of 158/100±5/2 mm Hg (mean±SEM) and a mean age of 53.9±2.5 years entered and completed the study, which was approved by the local hospital ethics committee.

Throughout the study, all subjects continued the above treatment with captopril (50 mg twice daily, Capoten, Squibb, Hounslow, England) and hydrochlorothiazide (25 mg once daily) initially on their usual diet. The patients studied had been assessed as hypertensive several weeks or months before entry to the study. Many patients alter their diet, including restricting salt intake, when high blood pressure is first diagnosed. The “usual diet” in the patients at entry to this study may therefore in many cases have included dietary sodium restriction. After 1 month of observation on their usual sodium intake, the subjects were then advised by the metabolic unit dietitian how to reduce their sodium intake to 80-100 mmol/tablet) for 1 month and 1 month of observation on their usual diet, the study had a power of greater than 90% at the 5% level to detect a 4 mm Hg difference in supine systolic and 3 mm Hg difference in supine diastolic pressure in response to sodium restriction with each order of starting treatment in the randomized double-blind study. After 4 weeks of treatment was checked by tablet count. Measurements were therefore free from observer bias. Supine and standing blood pressure, pulse rate, and weight were measured every 2 weeks, with each patient being seen in the same room, on the same day of the week, and at the same time of day. Blood pressure was measured in the same arm by nurses trained in the use of semiautomatic ultrasound sphygmomanometers (Arteriosonde, Roche, Cranbury, N.J.) with attached recorders. Measurements were therefore free from observer bias. Supine and standing blood pressure was taken as the mean of five recordings made at 1–2-minute intervals in each position. After 4 weeks of their usual diet, a 2-week run-in period of dietary sodium restriction, and each 4-week treatment period during the double-blind study of sodium restriction, patients were seen at 12 hours and 2 hours after their last dose of captopril and 24 hours and 2 hours after the last dose of hydrochlorothiazide. Patients were seen before their morning dose of tablets, having taken their usual dose of captopril the night before and their usual dose of hydrochlorothiazide the previous morning.

Blood pressure, pulse rate, and weight were then measured 12 hours after the last dose of tablets, as well as 2 hours after supervised treatment with the morning dose of tablets. Blood samples were taken after 5 minutes of sitting rest, 2 hours after the last dose of captopril and hydrochlorothiazide, for measurement of plasma electrolytes, creatinine, urca, uric acid, and full blood count, 2 and 12 hours after the previous dose of captopril, and 2 and 24 hours after the previous dose of hydrochlorothiazide for measurement of plasma renin activity and aldosterone. During the study, before each visit, patients collected two consecutive 24-hour urine samples for measurement of 24-hour urinary sodium, potassium, creatinine, and volume. Compliance with captopril, hydrochlorothiazide, Slow Sodium, and placebo treatment was checked by tablet count.

Mean arterial pressure was calculated by adding one third of the pulse pressure to the diastolic pressure. Results are reported as mean±SEM unless otherwise indicated. Statistical analysis was performed by paired Student's t test and Pearson's correlation analysis, using the Northwestern University Statistical Package for Social Sciences on the University of London computer. The changes in blood pressure with sodium restriction during the double-blind study were also analyzed by two-way analysis of variance (ANOVA) for repeated measurements. Where significant differences were found using ANOVA, paired measurements were then compared by t test, using the least significant difference derived from the pooled error variance (ANOVA). The method of Hills and Armitage was used to test for treatment period interaction. For a sample size of 10 subjects in each group and for a two-tailed t test, the study had a power of greater than 90% at the 5% level to detect a 4 mm Hg difference in supine systolic and 3 mm Hg difference in supine diastolic pressure in response to sodium restriction with each order of starting treatment in the randomized double-blind study.

Results

Blood Pressure 2 Hours After Treatment and Urinary Sodium Excretion

In the 21 patients, the average supine blood pressure after 1 month's observation on their usual diet, 2 hours after treatment with captopril (50 mg twice daily) and hydrochlorothiazide (25 mg once daily), was 147/96±5/3 mm Hg with a 24-hour urinary sodium excretion of 137±15 mmol (Figure 1). After 2 weeks of moderate sodium restriction combined with captopril and hydrochlorothiazide, supine blood pressure 2 hours after treatment was 135/89±4/2 mm Hg (24-hour urinary sodium excretion 108±12 mmol). Patients were then entered into the double-blind part of the study. After 4 weeks of treatment with Slow Sodium (100 mmol/day), captopril, and hydrochlorothiazide, supine blood pressure 2 hours after treatment was 147/91±5/2 mm Hg (24-hour
FIGURE 1. Graphs showing average supine systolic and diastolic blood pressure and urinary sodium excretion on captopril (50 mg twice daily) and hydrochlorothiazide (25 mg once daily) after 1 month's observation on normal diet, 2 weeks open study on dietary sodium restriction, and at the end of each month of the randomized crossover trial of Slow Sodium tablets compared with matching placebo. ANOVA: supine systolic blood pressure treatment effect F=13.71, p=0.001, time effect F=30.43, p<0.001; supine diastolic pressure, treatment effect F=8.8, p<0.01, time effect F=34.8, p<0.001). *p<0.05, **p<0.01, ***p<0.001 comparing measurements at 2 hours and 12 hours after treatment; \*p<0.05 comparing measurements on normal diet and after 2 weeks of sodium restriction; \*\*p<0.01, \*\*\*p<0.001 comparing measurements on Slow Sodium and on placebo.

urinary sodium 195±14 mmol). After 4 weeks of Slow Sodium placebo, captopril, and hydrochlorothiazide, average supine blood pressure 2 hours after treatment was 138/88±5/2 mm Hg (24-hour urinary sodium 104±11 mmol). The fall in supine systolic blood pressure from Slow Sodium to placebo tablets was 9±3 mm Hg (p<0.01) and 3±2 mm Hg (NS) in supine diastolic pressure. The reduction in urinary sodium excretion of 91±12 mmol for 1 month was associated with a decrease in supine mean arterial pressure of 5±2% 2 hours after treatment with captopril and hydrochlorothiazide (p<0.05). There was no significant treatment period interaction in the double-blind part of the study for the changes in urinary sodium excretion, blood pressure, and blood measurements with moderate sodium restriction.

**Blood Pressure 12 Hours After Treatment**

Twelve hours after treatment with captopril and 24 hours after treatment with hydrochlorothiazide, after 1 month on their usual diet, the patients' average supine blood pressure was 155/100±5/2 mm Hg during the double-blind part of the study. After 4 weeks of Slow Sodium, supine blood pressure was 159/102±6/2 mm Hg, and after 4 weeks of Slow Sodium placebo, it was 148/95±5/2 mm Hg (Figure 1). In association with moderate sodium restriction, there were significant falls in both supine systolic (11±3 mm Hg, p<0.01) and diastolic (7±2 mm Hg, p=0.001) pressure with a 7±2% fall in mean arterial pressure.

**Heart Rate and Standing Blood Pressure**

There were no significant changes in supine or standing heart rate with moderate sodium restriction during the study (data not shown). The effects of moderate sodium restriction on standing blood pressure during the study were similar to the effects on supine blood pressure (Table 1). The changes in blood pressure with moderate sodium restriction during the double-blind part of the study were not affected by the order in which these treatments were assigned.

**Comparison of Blood Pressure 2 Hours and 12 Hours After Treatment**

During the double-blind part of the study, blood pressure was significantly lower at 2 hours compared with 12 hours after treatment, both after 4 weeks on Slow Sodium and after 4 weeks on Slow Sodium placebo. Supine blood pressure increased by 10/6±3/2 mm Hg (p=0.001/p<0.01) to 159/102±6/2 mm Hg from 2 to 12 hours after treatment with captopril and from 2 to 24 hours after hydrochlorothiazide after 4 weeks on Slow Sodium placebo and by 11/11±2/2 mm Hg (p=0.000/p=0.000) between the same times after treatment after 4 weeks on Slow Sodium tablets (Figure 1).

**Other Variables**

During the double-blind part of the study, with moderate sodium restriction, there were significant reductions in weight (Table 1), plasma sodium (1.8±0.7 mmol/l), and urine volume (0.24±0.10 l/24 hr) and significant increases in plasma creatinine (10.8±3.0 μmol/l) and uric acid (39±9 μmol/l) (Table 2). There was no significant change in plasma potassium, urea, albumin, or hematocrit (Table 2).

After treatment with captopril and hydrochlorothiazide, plasma renin activity and plasma aldosterone were significantly increased after 4 weeks of moderate sodium restriction compared with 4 weeks on Slow Sodium, both 2 and 12 hours after the last dose of tablets (Table 1). After 4 weeks of moderate sodium restriction combined with captopril and hydrochlorothiazide therapy, plasma renin activity was significantly higher and plasma aldo-
Sodium Restriction in Hypertension

TABLE 1. Standing Blood Pressure, Weight, Plasma Renin Activity, and Plasma Aldosterone Levels at the End of Each 4-Week Treatment Period

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Captopril (50 mg twice daily) + hydrochlorothiazide (25 mg once daily)</th>
<th>Sodium restriction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal diet</td>
<td>Slow Sodium</td>
</tr>
<tr>
<td>Standing systolic pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 hr</td>
<td>153±5</td>
<td>145±5*</td>
</tr>
<tr>
<td>2 hr</td>
<td>143±5†</td>
<td>145±6‡</td>
</tr>
<tr>
<td>Standing diastolic pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 hr</td>
<td>107±2</td>
<td>104±3</td>
</tr>
<tr>
<td>2 hr</td>
<td>101±2$</td>
<td>103±2‡</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.7±2.8</td>
<td>...</td>
</tr>
<tr>
<td>Plasma renin activity (nmol Ang I/l/hr)</td>
<td>2.86±0.51</td>
<td>6.44±1.75*</td>
</tr>
<tr>
<td>Aldosterone (pmol/1)</td>
<td>555±81</td>
<td>348±44*</td>
</tr>
</tbody>
</table>

Values are mean±SEM. n=21 patients. Analysis of variance: standing systolic blood pressure, treatment effect F=433, p>0.05; time effect F=14.36, p<0.001; standing diastolic pressure, treatment effect F=11.62, p<0.01; time effect F=28.52, p<0.001.

*p<0.05, †p<0.01, ‡p=0.001 comparing measurements 2 hours and 12 hours after treatment.

Steroid significantly decreased at 2 hours compared with 12 hours after the last dose of tablets (Table 1). There were similar findings after 4 weeks of Slow Sodium combined with captopril and hydrochlorothiazide therapy.

The reduction in blood pressure with moderate sodium restriction was positively correlated with the reduction in urinary sodium excretion (2 hours after treatment, r=0.53, p<0.05, Figure 2; 12 hours after treatment r=0.44, p<0.05, data not shown). All patients completed the study without adverse effects.

Discussion

This double-blind, randomized crossover study clearly shows that in patients with essential hypertension in whom the renin system is blocked by captopril, a reduction in sodium intake causes a fall in blood pressure, even when combined with a thiazide diuretic. The fall in blood pressure was of a similar order to that seen with sodium restriction alone,12 a β-blocker, or a diuretic alone15 in patients with essential hypertension. Dietary sodium restriction increased the efficacy of captopril at the time of maximal action, 2 hours after treatment. In addition, the blood pressure before the morning dose of treatment was lower with sodium restriction, and there was a greater lowering of blood pressure at the trough compared with the peak effect of the captopril treatment. Thus, sodium restriction was both synergistic with treatment, as well as extending the duration of action of the combination of captopril and hydrochlorothiazide.

An important question is whether the reduction in average sodium intake during the double-blind part of the present study from 195 to 104 mmol/day is relevant to current levels of sodium intake in populations in which hypertension is prevalent. In the Scottish heart health study, the average sodium intake reported in 3,754 men was 192.8±76.7 (SD) mmol/24 hr.16 In the multinational INTERSALT

TABLE 2. Other Blood and Urinary Measurements During the Study

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Captopril (50 mg twice daily) + hydrochlorothiazide (25 mg once daily)</th>
<th>Sodium restriction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal diet</td>
<td>Slow Sodium</td>
</tr>
<tr>
<td>Sodium (mmol/l)</td>
<td>138.9 (0.8)</td>
<td>139.4 (0.8)</td>
</tr>
<tr>
<td>Potassium (mmol/l)</td>
<td>3.6 (0.1)</td>
<td>3.7 (0.1)</td>
</tr>
<tr>
<td>Urea (mmol/l)</td>
<td>6.9 (0.4)</td>
<td>6.4 (0.4)</td>
</tr>
<tr>
<td>Creatinine (μmol/l)</td>
<td>86 (6)</td>
<td>91 (6)</td>
</tr>
<tr>
<td>Uric acid (μmol/l)</td>
<td>414 (19)</td>
<td>378 (19)</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>41.8 (0.8)</td>
<td>40.5 (0.9)</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>44 (1)</td>
<td>44 (1)</td>
</tr>
<tr>
<td>Urinary potassium (mmol/24 hr)</td>
<td>63 (4)</td>
<td>72 (5)</td>
</tr>
<tr>
<td>Urinary creatinine (mmol/24 hr)</td>
<td>13.4 (1.0)</td>
<td>13.3 (1.1)</td>
</tr>
<tr>
<td>Volume (l)</td>
<td>1.52 (0.09)</td>
<td>1.84 (0.12)</td>
</tr>
</tbody>
</table>

Values are mean±SEM.

*p<0.05, †p<0.01, ‡p<0.001 after 4 weeks of placebo compared with 4 weeks of Slow Sodium while patients were treated with captopril (50 mg b.i.d.) and hydrochlorothiazide (25 mg o.d.).
In mean arterial pressure (mmHg)

Decrease in urinary sodium (mmol/24hr)

-20 0 20 40 60 80 100 120 140 160 180 200 220

-15 -10 -5 0 5 10 15 20 25 30

FIGURE 2. Scatterplot showing reduction in 24-hour urinary sodium from the fourth week of Slow Sodium to the fourth week of placebo, 2 hours after captopril (50 mg twice daily) and hydrochlorothiazide (25 mg once daily) \( t=0.53, p<0.05 \).

study of 10,079 adults, 34 of the 52 centers had an average sodium excretion for men and women greater than 150 mmol/24 hr, and in 19 of the 52 centers, it was greater than 170 mmol/24 hr. These recently published epidemiological data indicate that the sodium excretion of 195 ±14 (SEM) mmol/24 hr in the double-blind part of the present study was comparable with the usual intake in many communities both in the United Kingdom as well as in other countries.

With moderate sodium restriction alone, the degree to which blood pressure falls appears to be dependent on the extent to which reactive mechanisms blunt the response to a reduction in intravascular sodium and water. In particular, there is a compensatory rise in renin1-4 and thus, circulating angiotensin II. This increase in angiotensin II can be blocked by the addition of an inhibitor of the renin-angiotensin-aldosterone system18 so that blood pressure then becomes much more dependent on sodium and water balance. This concept was supported by two previous studies in which it was found that in patients with essential hypertension in whom the renin system is blocked by captopril6 or enalapril,7 moderate sodium restriction results in a further fall in blood pressure. Furthermore, with sodium restriction alone, there is no relation between changes in sodium balance and the degree to which blood pressure falls,1-3 whereas when the renin system is blocked, the change in blood pressure is significantly correlated with the change in dietary sodium intake.6

Treatment with angiotensin converting enzyme inhibitors alone does not always control blood pressure in patients with moderate-to-severe essential hypertension. The addition of a thiazide diuretic to angiotensin converting enzyme inhibitor treatment has been shown to be effective in reducing blood pressure to the desired range in many patients with more severe essential hypertension.8-10 This further fall in blood pressure with the addition of a thiazide8-10 appears to be similar to the fall in blood pressure with the addition of sodium restriction to a converting enzyme inhibitor.6,7 However, blood pressure is not always controlled with this combination of a converting enzyme inhibitor and a thiazide. Increasing the dose of diuretic will cause a further fall in blood pressure but is associated with greater adverse metabolic effects even in the presence of a converting enzyme inhibitor.9 In contrast, moderate sodium restriction alone,1,2 as well as when added to previous treatment with a converting enzyme inhibitor,5,7 does not appear to be associated with significant adverse metabolic effects. The present study suggests that the addition of moderate sodium restriction to the combination of a converting enzyme inhibitor and a thiazide is not associated with significant changes in plasma potassium or urea and may be associated with an increase of around 10% in plasma uric acid and creatinine to average values within the normal laboratory range for these measurements.

The further fall in blood pressure with the addition of sodium restriction to the combination of a converting enzyme inhibitor and a thiazide is consistent with previous studies of sodium restriction with regard to the additive effects both at peak and trough actions of the treatment. The blood pressure before the morning dose of treatment was lower when patients were on Slow Sodium placebo compared with when they were on Slow Sodium supplements. Thus, blood pressure was lower and there was less variation in peak and trough blood pressure when patients were on mild dietary sodium restriction. This additive effect of sodium restriction on the trough effect of treatment for blood pressure is likely to be largely due to additive effects of sodium restriction on the actions of the thiazide since this and previous reports indicate that captopril is relatively short acting.19 This additive effect of sodium restriction and diuretic treatment is consistent with our previous report of a linear dose response of blood pressure to sodium restriction in the range from 200 down to 50 mmol/day in patients with essential hypertension on dietary sodium restriction alone,20 so that the greater the lowering of sodium intake, the greater the fall in blood pressure. Furthermore, when the renin system is blocked by an angiotensin converting enzyme inhibitor, blood pressure becomes dependent on sodium intake, the reduction in blood pressure becom-
ing proportional to the degree to which subjects are able to reduce their dietary sodium intake.\(^6\)

Our study clearly demonstrates an additive effect on blood pressure of moderate sodium restriction when combined with a converting enzyme inhibitor and a thiazide. A number of studies now indicate that in both hospital practice\(^1,2,20\) as well as the community,\(^21\) the moderate sodium restriction achieved in this study is practical and well tolerated by most patients. The results of the present study suggest that in patients with moderate-to-severe hypertension in whom blood pressure is not controlled by the combination of a converting enzyme inhibitor and hydrochlorothiazide and who are prepared to restrict their sodium intake moderately, this combination may provide an effective way to improve blood pressure control, with a reduction in blood pressure and less variation in the peak and trough response to the above treatment.

References
\(^14\) Hills M, Armitage P: The two-period cross-over clinical trial. \textit{Br J Clin Pharmacol} 1979;8:7–20

\textbf{KEY WORDS}: essential hypertension, diet, sodium-restricted, renin-angiotensin-aldosterone system, thiazide diuretics, angiotensin converting enzyme inhibitors
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