The blunting of the antiproteinuric efficacy of ACE inhibition by high sodium intake can be restored by hydrochlorothiazide

Hanneke Buter¹, Marc H. Hemmelder¹, Gerjan Navis¹,², Paul E. de Jong¹ and Dick de Zeeuw¹,²

Groningen Institute for Drug Studies (GIDS)*, Divisions of ¹Nephrology and ²Clinical Pharmacology, State University Hospital, Groningen, The Netherlands

Abstract

Background. Dietary sodium restriction enhances the antiproteinuric and blood pressure lowering effect of ACE inhibition. In clinical practice, however, long-term compliance to a low-sodium diet may be difficult to obtain. We therefore investigated whether the blunting of the antiproteinuric and blood pressure lowering efficacy of ACE inhibition by high sodium intake can be restored by the addition of a diuretic.

Patients and methods. Seven proteinuric patients with non-diabetic renal disease on chronic ACE inhibition were studied during three consecutive 4-week periods: low sodium (50 mmol/day), high sodium (200 mmol/day) and high sodium plus hydrochlorothiazide (50 mg o.i.d.).

Results. During low sodium intake proteinuria was 3.1 (0.7–5.2) g/day, during high sodium intake proteinuria increased to 4.5 (1.6–9.2) g/day (P < 0.05). Interestingly, addition of hydrochlorothiazide again reduced proteinuria to 2.8 (0.6–5.8) g/day (P < 0.05). Mean arterial blood pressure was 89 (84–96), 98 (91–104) and 89 (83–94) mmHg (P < 0.05) during the three periods, respectively.

Conclusion. Addition of hydrochlorothiazide can overcome the blunting of the therapeutic efficacy of ACE inhibition on proteinuria and blood pressure by a high sodium intake.

Key words: ACE inhibition; hydrochlorothiazide; non-diabetic renal disease; proteinuria; sodium restriction

Introduction

Proteinuria and high blood pressure are important risk factors for cardiovascular and renal morbidity and mortality [1–3]. Intervention in the renin–angiotensin system by angiotensin converting enzyme (ACE) inhibitors has proven to be the most effective strategy to lower both blood pressure and proteinuria in proteinuric patients [4]. Unfortunately, the response to ACE inhibition is blunted by a liberal sodium intake. Thus, in patients unable to comply with long-term dietary sodium restriction the antiproteinuric and blood pressure response to ACE inhibition is blunted [5,6]. Co-treatment with diuretics has been recommended to enhance the therapeutic benefits of ACE inhibition. Whereas additive antihypertensive effects of diuretics during ACE inhibition have been demonstrated [7], thus far no data are available on the effects of this combination on proteinuria.

In this study we investigated whether co-treatment with a diuretic can compensate for the blunting of the therapeutic response to ACE inhibition caused by poor compliance to dietary sodium restriction in proteinuric patients. For this purpose we studied blood pressure and antiproteinuric responses in seven proteinuric patients on chronic ACE inhibitor treatment during a sodium restricted diet, a high sodium diet and during subsequent addition of hydrochlorothiazide during a high sodium diet.

Patients and methods

Patients were eligible for the study when they had stable proteinuria of more than 1 g/day and a creatinine clearance of more than 30 ml/min during chronic ACE inhibitor treatment.

ACE inhibitors were continued in a fixed dose throughout the study. All other antihypertensive or diuretic treatment was withdrawn at least 4 weeks before the start of the study. The study consisted of three 4-week ambulatory periods: a low-sodium period, a high-sodium period and a high-sodium + hydrochlorothiazide period. The patients were instructed by a dietician to use a diet constant in protein (0.8–1.0 g/kg body weight/day) and in sodium (50 mmol/day) during the entire study. During the high-sodium and high-sodium + hydrochlorothiazide periods patients added three cups of vegetable soup and two sachets of salt to their usual diet, resulting in a sodium intake of 200 mmol/day. During the high-sodium + hydrochlorothiazide period, hydrochlorothia-
zide (50 mg once daily) was added. At the end of each period patients visited our outpatient clinic for blood pressure measurements and blood sampling. Before each visit patients collected three consecutive 24-h urine samples for determination of the urinary excretion of protein, sodium, creatinine and urea.

To exclude a possible time-dependent effect, we also analysed data obtained during a regular outpatient clinic visit 3 months after the end of this non-randomized study. All data were obtained in the same way as during the study, except for the fact that patients collected only one 24-h urine sample.

Blood pressure was measured after 10 min supine rest at 1-min intervals during 5 min using an automated device (Dinamap®). The mean of the three intermediate readings was recorded. Mean arterial pressure (MAP) was calculated as the sum of one-third systolic and two-thirds diastolic blood pressure. Urinary protein was determined using the pyrogallol red–molybdate method [8]. Proteinuria is expressed both as an absolute amount as g/24 h and as fractional protein excretion, i.e. mg/ml creatinine clearance. Serum and urinary electrolytes, urea and creatinine were determined using an automated multi-analyser (SMA-C, Technicon®). The mean of three measurements was used for data analysis.

Results are expressed as median and 95% confidence intervals (95% CI). Statistical analysis was performed using the Wilcoxon rank-sign test for paired, non-parametric data. Statistical significance was assumed at 5% level.

Results

We included seven patients during chronic ACE inhibitor treatment (mean duration 33 months) and chronic dietary advice of 50 mmol sodium per day (Table 1). In all patients ACE inhibition had lowered proteinuria, from a median of 7.3 (3.8–9.0) g/day before the onset of treatment to 2.9 (1.4–5.6) g/day (P < 0.05) before the start of the present study. MAP was lowered from 100 (89–122) mmHg to 86 (81–93) mmHg (P < 0.05). One patient (No. 2) used diuretics prior to the study, after 4 weeks' withdrawal of this medication proteinuria increased from 4.0 to 8.0 g/day.

Urinary sodium excretion was 100 (67–111) mmol/day during the low-sodium period, indicating an adequate but moderate dietary compliance. During the high-sodium and subsequent hydrochlorothiazide period urinary sodium excretion amounted to 178 (158–212) and 180 (156–208) mmol/day, respectively. Urinary urea excretion did not change significantly during the study with values of 338 (286–383), 329 (287–408) and 360 (307–439) mmol/day, respectively, reflecting a stable protein intake. During the low-sodium period proteinuria was 3.1 (0.7–5.2) g/day and MAP was 89 (83–96) mmHg. High sodium intake resulted in an increase in proteinuria and blood pressure in six out of seven patients, resulting in a median proteinuria of 4.5 (1.6–9.2) g/day (P < 0.05 vs low sodium) and a MAP of 98 (91–104) mmHg (P < 0.05 vs low sodium). Interestingly, the addition of hydrochlorothiazide restored the responses of proteinuria and blood pressure to values of 2.8 (0.6–5.8) g/day (P < 0.05 vs high sodium) and 89 (83–94) mmHg (P < 0.05 vs high sodium), respectively (Figure 1). To correct for possible changes in glomerular filtration we calculated the fractional clearance of protein. During the low-sodium period the fractional protein filtration was $23 \times 10^{-3}$ mg/ml, during the high-sodium period $53 \times 10^{-3}$ mg/ml and after the addition of hydrochlorothiazide $28 \times 10^{-3}$ mg/ml (P < 0.05 vs high sodium). Bodyweight was 82.2 (71.1–88.6) kg during the low-sodium period and 82.6 (71.9–89.1) kg during the high-sodium period. The addition of hydrochlorothiazide resulted in a slight but significant decrease in bodyweight to 82.1 (70.8–88.3) kg (P < 0.01). Creatinine clearance was 75 (43–96) ml/min during the low-sodium period, 80 (45–104) ml/min during the high-sodium period, and tended to be slightly lower with a median value of 61 (41–94) ml/min after the addition of hydrochlorothiazide (n.s.). The slight changes in serum potassium [5.4 (4.7–5.5) mmol/l during low sodium, 4.9 (4.4–5.6) mmol/l during high sodium and 4.6 (4.5–5.1) mmol/l after the addition of hydrochlorothiazide] and uric acid [0.47 (0.39–0.58), 0.44 (0.38–0.53) and 0.52 (0.43–0.61) mmol/l] during the three periods, respectively, did not reach statistical significance in this small group of patients.

Table 1. Patient characteristics before the start and after stabilization on monotherapy ACE inhibition

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>Creatinine clearance (ml/min)</th>
<th>Proteinuria (g/day)</th>
<th>MAP (mmHg)</th>
<th>Medication</th>
<th>ACE inhibition therapy (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64</td>
<td>m</td>
<td>FSGS</td>
<td>97</td>
<td>2.9</td>
<td>82</td>
<td>ena 10 mg</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>f</td>
<td>MGP</td>
<td>110</td>
<td>8.0</td>
<td>89</td>
<td>ena 10 mg</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>53</td>
<td>m</td>
<td>MGP</td>
<td>85</td>
<td>4.4</td>
<td>99</td>
<td>lis 10 mg</td>
<td>54</td>
</tr>
<tr>
<td>4</td>
<td>32</td>
<td>m</td>
<td>IgA</td>
<td>69</td>
<td>3.5</td>
<td>93</td>
<td>lis 10 mg</td>
<td>48</td>
</tr>
<tr>
<td>5</td>
<td>53</td>
<td>m</td>
<td>IgA</td>
<td>33</td>
<td>1.2</td>
<td>94</td>
<td>ena 5 mg</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>47</td>
<td>m</td>
<td>FSGS</td>
<td>87</td>
<td>2.9</td>
<td>83</td>
<td>ena 10 mg</td>
<td>33</td>
</tr>
<tr>
<td>7</td>
<td>52</td>
<td>m</td>
<td>HN</td>
<td>51</td>
<td>1.5</td>
<td>91</td>
<td>ena 5 mg</td>
<td>14</td>
</tr>
<tr>
<td>Median</td>
<td>52</td>
<td>1f/6m</td>
<td></td>
<td>85</td>
<td>2.9</td>
<td>91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>40–58</td>
<td></td>
<td></td>
<td>51–101</td>
<td>1.4–5.6</td>
<td>85–96</td>
<td></td>
<td>13–46</td>
</tr>
</tbody>
</table>

FSGS = focal segmental glomerulosclerosis; MGP = membranous glomerulopathy; IgA = IgA nephritis; HN = hypertensive nephrosclerosis; ena = enalapril; lis = lisinopril.
the patients developed oedema or gout during the study.

Three months after the end of the study patients visited the out-patient clinic. At this time patients used the same medication as before start of the study. Proteinuria was 3.3 (1.2–4.8) g/day and MAP 88 (83–96) mmHg. The fractional protein filtration was \(25 \times 10^{-3}\) mg/ml, urinary sodium excretion 107 (68–155) mmol/l, the creatinine clearance was 73 (44–101) ml/min. None of these parameters were significantly different from data obtained before the start of the study.

**Discussion**

The present study confirms that in patients on chronic ACE inhibitor treatment, the antiproteinuric and blood pressure lowering effect of ACE inhibition is blunted by or even lost during a high sodium intake [5,6,9]. In clinical practice, co-treatment with diuretics is often recommended to enhance the antihypertensive effects of ACE inhibition, but the additive effects of diuretics and ACE inhibition had not been demonstrated in proteinuric patients. Interestingly, in the present study we found that during high sodium intake the antiproteinuric as well as the blood pressure response to ACE inhibition is restored by co-treatment with hydrochlorothiazide. The improvement in the blood pressure response during hydrochlorothiazide may have contributed to the reduction in proteinuria. However, our study was not designed to unravel the mechanism of the antiproteinuric effect, but merely to investigate whether the effects of dietary non-compliance could be overcome by the addition of hydrochlorothiazide. We did not investigate the effect of another blood pressure lowering agent on proteinuria, so we cannot provide a reliable estimate of the contribution of the lowering of blood pressure to the antiproteinuric efficacy found in the present study. In previous studies performed with agents such as betablockers and calcium channel antagonists a blood pressure lowering response of \(\sim 12\%\) has been shown to correspond to a reduction in proteinuria of \(\sim 15\%\) [10]. In the present study, the addition of hydrochlorothiazide resulted in a reduction in blood pressure of 10% whereas the reduction in proteinuria was almost 40%. This finding suggests that the antiproteinuric effect found after the addition of hydrochlorothiazide to an ACE inhibitor cannot be explained solely by blood pressure lowering.

The use of diuretics is associated with a number of metabolic side-effects. In this small study the changes in biochemical parameters during the addition of hydrochlorothiazide did not reach statistical significance. To assess whether such changes have clinical relevance larger and more long-term studies would be required. Recent studies support the notion that not only lowering blood pressure, but also reduction of proteinuria per se is important to improve long-term renal prognosis in proteinuric patients [2,11–14]. Thus any effort should be made to ensure an optimal therapeutic response. Earlier studies have revealed that an optimal response can be achieved by dietary sodium restriction, but long-term compliance is often difficult to obtain. Another possibility for improving antiproteinuric efficacy, currently under study, is the combination of ACE inhibitors and AT-1 receptor antagonists. In conclusion, the addition of hydrochlorothiazide restores the responses of proteinuria and blood pressure to chronic ACE inhibition in proteinuric patients in whom the therapeutic response has been blunted by a high sodium intake. These findings, albeit in a small group of patients, provide an outlook on more effective reduction of proteinuria and also blood pressure as
major risk factors and may be of particular importance for the future design of renal and cardiovascular protection studies using intervention strategies in the renin–angiotensin system.

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References


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