Angiotensin II antagonism Improves the lipoprotein profile in patients with nephrotic syndrome

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Objective: To study the effects of the angiotensin II receptor antagonist losartan on the lipid profile of patients with nephrotic range proteinuria.

Design: A single-blind, longitudinal study. Patients were followed during four periods each lasting 1 month, in which they received in sequence once-daily placebo, 50 mg losartan, 100 mg losartan and placebo, respectively. Measurements were performed at the end of each study period.

Patients: Eleven patients with biopsy-proven renal disease, diastolic blood pressure ≥90 mmHg, creatinine clearance ≥50 ml/min, stable proteinuria ≥2.5 g/day, without familial hyperlipidemia or use of hypolipidemic agents.

Results: At the end of the 100 mg losartan period, median arterial blood pressure had fallen from 114.5 ± 2.3 mmHg at baseline to 96 ± 2.8 mmHg (P < 0.001). Urinary protein excretion decreased from 6.2 ± 1.3 g/day to 4.2 ± 1.3 g/day (P < 0.001), whereas serum albumin and total protein did not change. Total cholesterol fell significantly from 6.67 ± 0.46 mmol/l to 6.08 ± 0.42 mmol/l (P = 0.04). This decrease in cholesterol was mainly due to a decrease in very-low-density and low-density lipoprotein cholesterol, though high-density lipoprotein cholesterol also tended to fall. Apolipoprotein B decreased by 13.0 ± 3.6% (P = 0.05), whereas the apolipoprotein A1 concentration remained unchanged, thus resulting in a significant increase in the apolipoprotein A1/B ratio (12.5 ± 3.5%, P = 0.05). Lipoprotein(a) concentration fell from 287 ± 57 mg/l to 218 ± 35 mg/l (P = 0.07). Interestingly, those patients that had the highest baseline lipoprotein(a) values showed the most outspoken change in lipoprotein(a) levels during treatment. In the placebo recovery period all parameters returned towards baseline values.

Conclusions: In addition to lowering blood pressure and proteinuria, the angiotensin II antagonist losartan improves the lipoprotein profile in patients with nephrotic range proteinuria.

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Keywords: Albumin, angiotensin II, angiotensin II antagonist, kidney disease, lipoproteins, lipoprotein(a), nephrotic syndrome, proteinuria.

Introduction

The nephrotic syndrome is associated with changes in serum lipid profile. Among these changes are an increase in serum total cholesterol, very-low- and low-density-lipoprotein (VLDL and LDL) cholesterol, triglycerides and lipoprotein(a) [Lp(a)] [1–5]. These lipid abnormalities are generally considered to increase the risk of atherosclerosis development. Indeed, a high prevalence of coronary heart disease has been observed in this patient category [6].

Pharmacologic treatment of patients with the nephrotic syndrome has traditionally focused on the effects of drug intervention on proteinuria. As yet, little attention has been paid to treatment of other symptoms, such as the lipid abnormalities.

Recently, losartan, a new antihypertensive agent, has become available for clinical use. This drug is a specific antagonist of angiotensin II type 1 receptor. We previously reported that losartan lowers blood pressure, induces renal vasodilatation, and reduces urinary protein loss in
hypertensive patients with nephrotic range proteinuria [7]. Because of these qualities, losartan may prove to be of clinical value in the treatment of nephrotic patients. To investigate the possible effects of losartan on the serum lipid profile, we analyzed the lipid parameters of these patients at baseline, after 2-month losartan treatment and after drug withdrawal.

Methods

Patients and protocol

Eleven non-diabetic patients with biopsy-proven glomerulopathy participated in this study. Entry criteria were a diastolic blood pressure >90 mmHg, stable proteinuria in excess of 2.5 g/day, and creatinine clearance of more than 50 ml/min. Patients using other medication (including hypolipidemic agents and diuretics), or with a history of familial hyperlipidemia were not allowed to participate. All subjects gave informed consent to participate in the protocol, approved by the local Medical Ethical Committee.

This study was conducted in a single-blind, longitudinal design. Patients were followed during four study periods, each lasting 1 month. In the first period, patients received placebo once daily. In the second period patients were treated with losartan 50 mg once daily, titrated to 100 mg once daily in the third period. Finally, patients were studied during a recovery period after having received placebo once daily for 1 month. Measurements were performed at the end of the active treatment and placebo periods. Patients were instructed to take study medication daily at 0800 h, and to adhere to a diet containing 1 g protein per kg body weight and 100 mmol sodium per day. No dietary advice with regard to fat and cholesterol intake was given. At the end of all study periods patients collected three consecutive 24-h urine samples for measurement of proteinuria. After a 12-h fast, approximately 24 h after the last dose of medication, blood pressure was measured and venous blood was drawn for the determination of serum lipids and albumin.

Laboratory and clinical procedures

Venous blood was collected into vacuum tubes. Erythrocytes were removed by centrifugation at 3000 rpm for 15 min within 1 h after collection. Serum samples were frozen at -20°C until analyzed. Total cholesterol and triglycerides were assayed enzymatically. Cholesterol was measured in whole serum and in the high-density lipoprotein (HDL)-containing supernatant fraction after precipitation of apolipoprotein B-containing lipoproteins with polyethylene glycol-6000. VLDL and LDL lipids were calculated as the difference between plasma and the HDL-containing supernatant fraction. Apolipoproteins A1 and B were determined by immunoturbidimetry (Boehringer Mannheim, Germany, catalogue nos 726478 and 726494, respectively). Lip(a) levels were quantified using a commercially available enzyme-linked immunosorbent assay (Tint-Elize Lp(a), Biopool AB, Umeå, Sweden). All lipid and apolipoprotein determinations of each patient were assayed in one run. Laboratory determinations were carried out on blinded samples. Serum creatinine, total protein and albumin were measured on an SMA-C autoanalyzer. (Technicon Instruments Inc., Tarrytown, NY, USA). Urinary protein was determined by the pyrogallol-red-molybdate method, and blood pressure was recorded with the auscultatory method, using a Hawksley random-zero-sphygmomanometer. The first and fifth Korotkoff sounds were used for systolic and diastolic blood pressure, respectively. Mean arterial pressure was calculated as the sum of one-third of the systolic and two-thirds of the diastolic blood pressures.

Statistical analysis

Statistical analysis was performed using the commercially available computer software Confidence Interval Analysis and SPSS. Data are expressed as means ± SE, unless otherwise indicated. To test for differences between baseline placebo data and active treatment data, paired Student’s t-tests were used. To evaluate relationships between variables Pearson’s correlation coefficients were calculated. P<0.05 (two-sided) was considered to indicate statistical significance.

Results

Baseline characteristics of the patients (n=11; two females, nine males) were a mean age of 45 years (range 20–61 years), a systolic blood pressure of 154 mmHg (139–180 mmHg), diastolic blood pressure of 99 mmHg (91–111 mmHg), creatinine clearance of 87 ml/min (60–114 ml/min) and a mean urinary protein excretion of 5.8 g/24 h (2.5–14.4 g/24 h). Histologic diagnoses in these patients were glomerulosclerosis (four patients), membranous glomerulopathy (four patients) and one patient each with immunoglobulin (Ig)A nephropathy, membranoproliferative glomerulonephritis, and thin basement membrane disease.

The mean values of study parameters during the different phases of the protocol are given in Table 1, whereas data for individuals are shown in Figs 1 and 2. Losartan 100 mg once daily lowered blood pressure from baseline 114.5 ± 2.4 mmHg to 96.4 ± 3.0 mmHg (P<0.001). During active treatment, neither clinical nor laboratory adverse effects, such as symptomatic hypotension and hyperkalaemia, were noted. Urinary protein excretion had decreased significantly by 43 ± 7% (P<0.001) at the end of the active treatment period. As a result, serum albumin and total protein tended to rise, albeit not significantly (1.4 ± 1.8%, P=0.46, and 1.7 ± 1.2%, P=0.17, respectively).
Table 1. The effects of angiotensin II receptor antagonism in 11 patients with nephrotic range proteinuria.

<table>
<thead>
<tr>
<th>Mean arterial pressure (mmHg)</th>
<th>Placebo baseline (n=11)</th>
<th>Angiotensin II antagonist (n=11)</th>
<th>Placebo recovery (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria (g/24h)</td>
<td>6.2±1.3</td>
<td>4.1±1.3**</td>
<td>6.2±1.6</td>
</tr>
<tr>
<td>Serum albumin (g)</td>
<td>35.8±1.9</td>
<td>36.1±1.5</td>
<td>35.0±1.7</td>
</tr>
<tr>
<td>Serum total protein (g/l)</td>
<td>57.4±2.2</td>
<td>58.2±1.9</td>
<td>57.0±2.3</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>6.67±0.46</td>
<td>6.08±0.42*</td>
<td>6.56±0.48</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>2.25±0.60</td>
<td>2.38±0.73</td>
<td>2.60±0.93</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1.06±0.09</td>
<td>1.00±0.09</td>
<td>1.08±0.12</td>
</tr>
<tr>
<td>VLDL+LDL cholesterol (mmol/l)</td>
<td>5.61±0.51</td>
<td>5.08±0.46*</td>
<td>5.48±0.53</td>
</tr>
<tr>
<td>Apolipoprotein A1 (g/l)</td>
<td>1.71±0.12</td>
<td>1.64±0.10</td>
<td>1.69±0.11</td>
</tr>
<tr>
<td>Apolipoprotein B (g/l)</td>
<td>1.02±0.09</td>
<td>0.86±0.05*</td>
<td>0.97±0.10</td>
</tr>
<tr>
<td>Apolipoprotein A1/B</td>
<td>1.77±0.15</td>
<td>2.00±0.20*</td>
<td>1.83±0.15</td>
</tr>
<tr>
<td>Lipoprotein(a) (mg/l)</td>
<td>287±57</td>
<td>218±35</td>
<td>242±58</td>
</tr>
</tbody>
</table>

*Mean±SEM. HDL, high-density lipoprotein; VLDL, very-low-density lipoprotein; LDL, low-density lipoprotein. *P<0.05, **P<0.01, versus baseline.

Serum cholesterol fell from 6.67±0.46 mmol/l to 6.08±0.42 mmol/l during losartan treatment (P=0.04). This fall in cholesterol was predominantly caused by a decrease in VLDL and LDL cholesterol (~8.7±4.3%, P=0.07), though HDL cholesterol also tended to fall (~4.7±4.1%, P=0.28). Apolipoprotein B decreased by 13.0±3.6% (P=0.005), whereas apolipoprotein A1 remained unchanged (~2.0±5.3%, P=0.72), thus resulting in a significant increase in the apolipoprotein A1/B ratio (12.5±3.5%, P=0.005). Mean Lp(a) concentration in this group of proteinuric patients was 287±57 mg/l. For comparison, in our laboratory, mean Lp(a) concentration in a group of 29 healthy volunteers was found to be 71 mg/l (95% confidence interval 20–122 mg/l). Lp(a) concentration fell during treatment to 218±35 mg/l (P=0.07). Interestingly, those patients with the highest baseline Lp(a) values also showed the most outspoken changes in this lipoprotein (Fig. 2).

Baseline proteinuria correlated with baseline serum albumin concentration and triglyceride levels (r=0.70 and 0.60, respectively; both P<0.05), whereas baseline serum albumin levels correlated with total cholesterol, VLDL and LDL cholesterol, apolipoprotein B and the apolipoprotein A1/B ratio (r=0.60, 0.64, 0.64 and 0.66, respectively; all P<0.05). No significant correlations were found between changes in proteinuria or serum albumin and the various lipid parameters.

The observed changes in the lipoprotein profile during losartan were rather uniform, since nine out of 11 patients showed a clear and moreover reversible decrease in serum total cholesterol, VLDL and LDL cholesterol.
(Fig. 2) and apolipoprotein B. It is of note that, while 10 patients had an antiproteinuric response of at least 20%, one patient did not show a decrease in urinary protein excretion during losartan treatment. As can be seen in Fig. 2, this patient was also one out of the two non-responders with respect to the lipoprotein profile (dashed lines).

During the placebo recovery period, parameters returned towards baseline in most patients, indicating that changes during active treatment were indeed drug-related (Table 1, Figs 1 and 2). Recovery data could not be obtained from one patient who withdrew due to circumstances not related to the study.

**Discussion**

As we have reported previously, the angiotensin II antagonist losartan effectively lowers blood pressure and urinary protein excretion in patients with nephrotic range proteinuria [7]. The present study shows that losartan favorably affected the plasma lipid derangements in these patients. Serum total cholesterol was lowered, predominantly because of a decrease in the VLDL and LDL cholesterol fraction, although HDL cholesterol tended to fall as well. Apolipoprotein B decreased, whereas serum apolipoprotein A1 concentration remained unchanged, thus resulting in a significant increase in their ratio. Moreover, Lp(a) concentration fell, albeit non-significantly.

Treatment of the nephrotic syndrome is of clinical importance for several reasons. As well as benefitting patients by the reduction of edema, treatment may also reduce the increased risk of infections, thrombosis or coronary heart disease observed in this group [6]. Moreover, it has been suggested that the nephrotic condition increases the risk of progressive renal function loss [8,9]. The question of what causes the increased morbidity and mortality rates is not yet answered. Several factors have been suggested as likely candidates, such as urinary protein loss and changes in plasma lipids.

The increased risk of coronary heart disease in patients with the nephrotic syndrome has been attributed to a deranged lipid profile, that is an increase in LDL at VLDL cholesterol, but also in Lp(a) levels [2–5,10,11]. Both parameters have been shown to be independent risk factors for cardiovascular disease [12,13]. Interestingly, Lp(a) has also been linked to the development of thrombosis [14,15]. Thus, it seems plausible that the increased concentration of this lipoprotein may have a role in the increased risk for thrombo-embolic events in nephrotic patients.

The progressive loss of renal function observed in many of the proteinuric patients appears to be multifactorial. Besides a role of intraglomerular hemodynamic change, proteinuria has been implicated as a possible mediator of renal damage, mainly in experimental settings [16]. Lowering proteinuria may thus protect the kidney against further function loss. Indeed, several clinical studies have shown that proteinuria correlates with the rate of decline of renal function [8,17], and more importantly that reduction of proteinuria may result in a renal protective effect [18–22]. The exact role of proteinuria in the sequence of events leading to renal function loss is difficult to unravel, since changes in proteinuria are frequently associated with changes in serum lipids. Several animal studies have suggested that hyperlipidemia may also be important.
the progression of renal disease [23,24]. In these models antilipidemic agents have been effective in reducing renal injury, whereas dietary-induced hyperlipidemia increased the degree of renal damage. If these results can be shown to apply in humans, there may be a strong rationale for treating hyperlipidemia in patients with the nephrotic syndrome.

Several therapeutic approaches are available to date to reduce the above risk factors. First, reduction of urinary protein loss can be achieved with non-steroidal inflammatory drugs [25], a low-protein diet [26,27], ACE inhibitors [28] and, as we have shown, angiotensin II antagonists [7]. Specific intervention in the lipid metabolism of patients with the nephrotic syndrome has been studied in a number of clinical trials. Reducing dietary fat and cholesterol intake has been proven to be of limited value [23]. Similarly disappointing results were obtained with cholestyramine [29]. In contrast, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors cause a marked fall in serum total cholesterol [29–31]. Unfortunately, this latter class of drugs does not lower proteinuria in nephrotic patients, nor does it affect Lp(a) [30,31]. We have recently demonstrated that ACE inhibitors not only effectively lower proteinuria, but also lower total cholesterol and LDL levels. Intriguingly, when ACE inhibition was combined with another antiproteinuric treatment modality, a non-steroidal anti-inflammatory agent, not only was a further fall in proteinuria and cholesterol observed compared with monotherapy, but there was also a significant reduction in Lp(a) [5].

The present study demonstrates that losartan, the first clinically available representative of the angiotensin II antagonist class, has similar beneficial effects to ACE inhibitors in patients with nephrotic range proteinuria. We have previously demonstrated that losartan effectively lowers proteinuria, and that this antiproteinuric effect equals that of enalapril [32]. The present data show that losartan also had beneficial effects on the lipid profile in these patients, specifically by lowering VLDL and LDL cholesterol and improving the apolipoprotein A1/B ratio. However, the cholesterol lowering effect of the angiotensin II antagonist in our study is numerically not very impressive and appears to be less obvious than the reductions in cholesterol described with HMG-CoA reductase inhibitor therapy in the literature [29–31]. This may be due partly to the fact that baseline lipid derangements were mild and the active treatment duration of 8 weeks was relatively short. Of potential importance is our observation that losartan lowered Lp(a) levels in high pretreatment levels. The above findings obviously need further confirmation, preferably in patients with a more severe nephrotic condition, and after a longer treatment period.

Conclusions

In addition to lowering blood pressure and proteinuria, losartan improved lipid abnormalities in patients with nephrotic range proteinuria. Since the present and other studies indicate that the lipoprotein profile is not fully normalized with antiproteinuric treatment, the combination of antiproteinuric treatment and lipid lowering drugs may deserve further attention for the treatment of patients with the nephrotic syndrome. Whether the changes in lipid profile will eventually result in a better prognosis with regard to the incidence of cardiovascular disease, thrombosis or the development of glomerulosclerosis in these patients has yet to be proven.

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References


