Brief Report

The antiproteinuric effect of losartan is systemic blood pressure dependent

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Abstract

Background. It has been suggested that high doses of angiotensin II receptor antagonists (AIIAs) may reduce proteinuria by a non-haemodynamic action additional to their effect on systemic blood pressure.

Methods. We tested this for the AIIA losartan using a prospective single-blind randomized design in patients with proteinuria (>1 g/24 h) due to non-diabetic chronic renal failure (stable creatinine clearance >20 ml/min) and mild to moderate hypertension (130/80 < blood pressure < 160/110 mmHg). Twenty-one patients were randomized into two groups: group A received losartan 50 mg daily for 4 weeks, then 100 mg daily for 4 weeks; group B received losartan 50 mg daily for 8 weeks. Twenty-four hour ambulatory blood pressure and renal parameters were measured at baseline and at 4 and 8 weeks of treatment.

Results. Overall there was a 7 ± 2 mmHg fall (mean ± SEM) in mean daytime systolic blood pressure at 4 weeks, and a 22 ± 7% fall in protein/creatinine ratio (both $P < 0.05$), with no difference between groups A and B or between 4 and 8 weeks. These two changes were highly correlated ($r = 0.64, P = 0.006$, taking both groups together). Changes in diastolic pressure and in night-time systolic pressure did not reach statistical significance. Changes in renal plasma flow (measured by Tc 99m MAGIII), glomerular filtration rate and filtration fraction (measured by $^{51}$Cr EDTA) did not reach statistical significance, did not differ between the two groups and did not correlate with effects on proteinuria.

Conclusion. This study provides no evidence that the effect of losartan on proteinuria has a non-haemodynamic component.

Keywords: angiotensin II receptor antagonists; chronic renal failure; losartan; proteinuria; renal haemodynamics

Introduction

A clear relationship has been shown between progression of renal failure and the magnitude of proteinuria in a variety of renal diseases including glomerulonephritis and diabetic nephropathy [1]. Furthermore, treatment which reduces proteinuria retards the deterioration of renal function [2]. Angiotensin-converting enzyme inhibitors (ACEIs), by virtue of their ability to reduce proteinuria over and above their effect on systemic blood pressure (BP), have become the treatment of choice in diabetic nephropathy [3] and in some other proteinuric renal diseases [4]. The angiotensin II antagonist (AIIA) losartan has now been shown to have a similar effect [5] and, given their superior side effect profile, the increasing use of AIIAs in proteinuric diseases can be expected. Recently it has been suggested that higher doses of AIIAs may reduce proteinuria further by a non-haemodynamic action [5], raising the question of whether their therapeutic renoprotective dose might not be considerably higher than the conventional antihypertensive dose. This suggestion was based on the observation [5] that while losartan 50 mg daily reduced protein excretion by 31%, with a significant fall in systolic and diastolic BP, at a dose of 100 mg daily proteinuria fell by up to 46% but without additional fall in BP [5]. In this study, the maximal antiproteinuric effect was considered to have occurred by 3 weeks in each dosage regime, but patients were maintained on each dosage for only 4 weeks. The longitudinal crossover design of this study [5] could not exclude a slow, progressive fall in proteinuria...
beyond 4 weeks, which might be expected given experimental evidence that the antiproteinuric effect of AIIAs may be mediated in part by non-haemodynamic mechanisms such as remodelling of the renal microvasculature. This study [5] failed to show an additional antihypertensive effect of losartan 100 mg compared with 50 mg. However, another study [6] using 24 h ambulatory BP monitoring did identify an additional antihypertensive effect of losartan at 100 mg daily. However, patients in this study were studied only for 4 weeks [6].

We hypothesized that first, there may be a further reduction in proteinuria with 50 mg losartan beyond 4 weeks, and secondly, that this reduction in proteinuria with losartan 50 mg may be comparable with that achieved by losartan 50 mg for 4 weeks followed by losartan 100 mg for 4 weeks. Furthermore, we wished to investigate whether the antiproteinuric effects of these regimes were mediated by systemic BP, renal haemodynamics or haemodynamic-independent effects. We therefore investigated the effect of dose and duration of therapy on the efficacy of losartan on BP, renal haemodynamics and proteinuria, using an 8 week longitudinal study design.

Results

Twenty-one patients were randomized to take part in the study. Renal diagnoses were: idiopathic glomerulonephritis (n = 16), hypertensive nephrosclerosis (n = 2), chronic pyelonephritis (n = 1), proteinuria of uncertain aetiology (n = 2). Of these, four were excluded from follow-up (three with idiopathic glomerulonephritis and one with chronic pyelonephritis) for the following reasons: symptomatic hypotension; uncontrolled hypertension following randomization; a fall of proteinuria to <1 g/24 h on the day of commencing losartan; and non-compliance with treatment. This left eight patients in group A and nine patients in group B.

Table 1 gives mean values of the measurements at the start of the study and after 4 and 8 weeks of treatment for group A and group B. The only significant differences with time were in measures of proteinuria and of daytime arterial BP (systolic, diastolic and mean). To illustrate this, Figure 1 shows the complete time course of changes in clinic systolic and diastolic BPs (Figure 1A) and protein/creatinine ratio (Figure 1B): both showed significant changes with time (P = 0.001 and P = 0.02, respectively), but there were no significant differences between groups A and B (P = 0.6 and P = 0.8, respectively). The overall mean ± SEM changes at 4 weeks were 7 ± 2 mmHg in daytime ambulatory systolic pressure (P = 0.004) and 22 ± 7% in protein/creatinine ratio (P = 0.007); in neither case was there any significant change between 4 and 8 weeks. There were no significant changes in any night-time pressures. The changes in BP and proteinuria were correlated in individual patients: Figure 2 illustrates this with the significant correlation (r = 0.64 P = 0.006) between relative percentage changes in protein/creatinine ratio and ambulatory daytime mean arterial pressure (MAP). In a few subjects, daytime MAP and proteinuria only responded marginally to losartan, and, in one, daytime MAP significantly

Subjects and methods

Patients were selected from a population who regularly attended our renal out-patient unit. Entry criteria for the study were: non-diabetic chronic renal disease with mild to moderate hypertension (130/80 < BP < 160/110 mmHg); stable renal function (creatinine clearance > 20 ml/min) and stable proteinuria (>1 g/24 h); no immunosuppressive medication during the 3 months before and throughout the study. The patients were advised a diet containing 1 g protein per kg body weight and 100 mmol sodium per day. They were not taking antihypertensive medication prior to enrolment. Patients were randomized into two groups: group A, to receive losartan 50 mg daily for 4 weeks and then 100 mg daily for a further 4 weeks; and group B, to receive losartan 50 mg daily for 8 weeks. Patients were followed-up over a period of 8 weeks.

BP and 24 h urine (creatinine clearance, 24 h urinary protein) were measured prior to randomization and weekly thereafter. Before randomization and at 4 and 8 weeks, the following measurements were made. Renal haemodynamics were assessed by measurement of effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) using established radioisotopic techniques: ERPF was measured using Technetium-99m-labelled MAG III (mercaptoacetyltriglycercine) (Mallinkrodt Pharmaceuticals Petten, The Netherlands); GFR was measured using chromium-51 EDTA (Nycomed-Amersham Pharmacia, Amersham, UK). The radiation effective dose equivalent of the combined measurement was 0.054 mSv (within background levels). Both parameters are corrected for standard body surface area (1.73 m²). Twenty-four hour ambulatory BP was assessed using a Spacelab 2000 monitor, recording blood pressure every 30 min during the daytime and hourly at night. Blood was taken for determination of plasma renin activity and aldosterone, the patient having rested supine for 30 min before venesection.

Plasma renin activity was determined indirectly following generation of angiotensin I. The angiotensin thus generated was measured by radioimmunoassay using a solid-phase separation and 125I-labelled angiotensin I as tracer. The reagents were supplied by CIS Biointernational (Gif-sur-Yvette, France) and the assay is calibrated against MRC standard 71/328. Results are expressed as ng/ml/h. Plasma aldosterone is measured by a direct solid-phase radioimmunoassay using a ‘Coat-a-Count’ kit supplied by Diagnostic Products (Euro DPC, Llanberis, UK).

Data are expressed as mean ± SD or mean ± SEM as appropriate and as noted. Results were analysed for time dependence and differences between groups A and B by repeated-measures analysis of variance (ANOVA; SPSS), with post hoc analysis using Tukey’s test. Additionally, to illustrate the size of the effects, changes at 5 weeks (the end of the low-dose phase in group A) and 9 weeks (the end of the high-dose phase in group A, and the end of treatment in both groups) are expressed as mean ± SEM and their significance assessed by paired t-test.
increased, whilst proteinuria decreased. These observations are likely to represent the biological variation in the individual responses to losartan and, in the case where daytime MAP rose, non-compliance. Despite these considerations, daytime MAP correlated with proteinuria well across the group as a whole.

An apparent slight decrease in GFR, increase in ERPF and consequent decrease in filtration fraction did not reach statistical significance in either group, and there were no significant associations between these and the change in proteinuria. Apparent increase in mean plasma renin activity and decrease in plasma aldosterone did not reach statistical significance in either group (Table 1), nor did they correlate with changes in BP or urinary protein excretion.

Discussion

Angiotensin II blockade has an effect on proteinuria similar to that of ACE inhibition and probably has the same beneficial effects on progressive renal failure and vascular disease [5]. This antiproteinuric effect has been reported to be more than that expected from BP reduction alone [7–9]. Reduction in intraglomerular pressure, inferred from changes in renal haemodynamics, was thought initially to account for this. More recently, the anti-inflammatory action of angiotensin blockade has been cited as a mechanism for reductions in vascular morbidity and mortality [9,10], and a similar action may account in part for their antiproteinuric activity. However, in a number of comparative studies, there has been a statistically non-significant advantage in BP control with ACE inhibitors or angiotensin II blockers compared with other agents [9,10]. Furthermore, in early studies of the effect of inhibition of the renin–angiotensin system on proteinuria, the patients often had what we would now consider unacceptably high BP at outset. It still remains to be determined how much of the therapeutic benefit is related to BP and how much is due to other mechanisms. Gansevort et al. [5] support the concept of a non-haemodynamic component to the effects of AIIA on proteinuria. Using similar dosages of losartan but in a single-blind randomized design and monitoring 24 h ambulatory BP, we were unable to reproduce their findings. Given the patients’ renal impairment and modest hypertension at the start of the study, the BP response (7 ± 2 mmHg in daytime ambulatory systolic pressure) was in line with expectation. In line with current guidelines [11], our subjects had lower BP at the outset of the trial than Gansevort’s, and therefore the two studies may not be directly comparable. The 22% reduction in urinary protein/creatinine ratio was

Table 1. Measurements at start of study and 4 and 8 weeks of treatment in groups A and B (mean ± SD)

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Start 4 8</td>
<td>Start 4 8</td>
</tr>
<tr>
<td>Proteinuria</td>
<td></td>
<td></td>
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<tr>
<td>24 h urine protein (g)</td>
<td>3.5 ± 2.0 2.7 ± 1.7 2.6 ± 1.7</td>
<td>4.1 ± 2.9 3.2 ± 2.3 3.5 ± 2.2</td>
</tr>
<tr>
<td>Protein/creatinine (g:mmol)*</td>
<td>0.34 ± 0.22 0.28 ± 0.19 0.26 ± 0.19</td>
<td>0.35 ± 0.24 0.24 ± 0.16 0.27 ± 0.17</td>
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<tr>
<td>Serum/plasma</td>
<td></td>
<td></td>
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<tr>
<td>Serum urea (mmol/l)</td>
<td>7.9 ± 3.8 8.1 ± 4.3 8.3 ± 3.4</td>
<td>10.2 ± 4.1 10.6 ± 4.8 11.1 ± 3.8</td>
</tr>
<tr>
<td>Serum creatinine (mmol/l)</td>
<td>136 ± 62 135 ± 63 137 ± 62</td>
<td>161 ± 69 161 ± 69 170 ± 74</td>
</tr>
<tr>
<td>Serum Na (mmol/l)</td>
<td>141 ± 1 140 ± 1 139 ± 1</td>
<td>140 ± 2 140 ± 1 139 ± 3</td>
</tr>
<tr>
<td>Serum K (mmol/l)</td>
<td>4.5 ± 0.6 4.3 ± 0.8 4.3 ± 0.9</td>
<td>4.3 ± 0.5 4.3 ± 0.5 4.4 ± 0.7</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml/h)</td>
<td>1.4 (0.2–12) 3.6 (0.9–12) 1.8 (0.3–35)</td>
<td>2.0 (0.2–39) 1.6 (0.2–29) 1.6 (0.3–169)</td>
</tr>
<tr>
<td>Urine electrolytes</td>
<td></td>
<td></td>
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<tr>
<td>24 h urine Na (mmol)</td>
<td>170 ± 46 168 ± 44 165 ± 43</td>
<td>150 ± 55 160 ± 55 186 ± 40</td>
</tr>
<tr>
<td>24 h urine K (mmol)</td>
<td>59 ± 21 57 ± 20 61 ± 17</td>
<td>81 ± 22 70 ± 15 82 ± 24</td>
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<tr>
<td>Renal function</td>
<td></td>
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<tr>
<td>GFR (ml/min)</td>
<td>64 ± 33 61 ± 30 57 ± 26</td>
<td>50 ± 23 51 ± 25 49 ± 28</td>
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<tr>
<td>ERPF (ml/min)</td>
<td>251 ± 131 293 ± 175 281 ± 161</td>
<td>168 ± 56 216 ± 113 196 ± 73</td>
</tr>
<tr>
<td>Filtration fraction</td>
<td>0.26 ± 0.07 0.21 ± 0.03 0.22 ± 0.06</td>
<td>0.26 ± 0.06 0.24 ± 0.04 0.25 ± 0.08</td>
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<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
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<tr>
<td>Day</td>
<td></td>
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<tr>
<td>Systolic*</td>
<td>137 ± 19 128 ± 15 124 ± 18</td>
<td>136 ± 13 130 ± 11 130 ± 11</td>
</tr>
<tr>
<td>Diastolic*</td>
<td>85 ± 13 78 ± 11 76 ± 13</td>
<td>83 ± 8 81 ± 11 78 ± 7</td>
</tr>
<tr>
<td>MAP*</td>
<td>102 ± 14 95 ± 12 92 ± 14</td>
<td>101 ± 8 97 ± 10 95 ± 6</td>
</tr>
<tr>
<td>Night</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>117 ± 18 113 ± 18 110 ± 9</td>
<td>129 ± 18 121 ± 14 116 ± 13</td>
</tr>
<tr>
<td>Diastolic</td>
<td>76 ± 12 67 ± 11 66 ± 9</td>
<td>76 ± 11 75 ± 14 68 ± 10</td>
</tr>
<tr>
<td>MAP</td>
<td>90 ± 13 83 ± 13 81 ± 8</td>
<td>94 ± 12 90 ± 13 84 ± 10</td>
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within, but towards the lower end of, the range in other studies [4]. However, the reduction in proteinuria at 8 weeks was similar in patients who received losartan 50 mg throughout and those whose dose was doubled from 4 weeks. It is of note that, in both groups, there was a tendency for proteinuria to rise towards the end of the study period. This could have been due, in principle, to poor patient compliance. Although compliance was not measured by pill counting, we believe that it is unlikely to be significant. Despite the small absolute changes recorded, we found a strong correlation between reduction in proteinuria in individual patients and the reduction in mean ambulatory BP, particularly mean daytime systolic pressure. Treatment was very well tolerated, with only one patient withdrawn due to drug side effects (symptomatic hypotension). These findings are consistent with those of Bidani et al., who showed, in a rat model of chronic renal failure, that the renoprotective properties of both losartan and the ACEI benazepril were mediated primarily by systemic BP [12].

In conclusion, the antihypertensive effect of losartan appears to be the major factor in reducing proteinuria, rather than renal haemodynamic and non-haemodynamic effects. The study does not exclude other actions, but underlines the importance of lowering BP even when it is within what is currently regarded as acceptable. Patients with proteinuria and renal impairment are at high risk of disease progression and cardiovascular morbidity. The BP targets should be in line with those recommended for patients with diabetic renal disease. Losartan can be safely used and is effective in this context.

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Conflict of interest statement. None declared.

References


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