Randomized controlled crossover study of the effect on proteinuria and blood pressure of adding an angiotensin II receptor antagonist to an angiotensin converting enzyme inhibitor in normotensive patients with chronic renal disease and proteinuria

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Abstract

Background. Proteinuria and hypertension have independent deleterious effects on the progression of chronic renal disease. The objectives of this study were to determine whether the addition of Candesartan, an angiotensin II receptor antagonist, would reduce proteinuria and blood pressure in normotensive patients with chronic renal disease already receiving an angiotensin converting enzyme inhibitor (ACEI).

Methods. This was an open randomized controlled crossover study conducted in a private consultant practice in Melbourne. Sixty patients, aged 23–75, who had chronic renal disease and stable proteinuria over 0.5 g in 24 h and were receiving an ACEI, were enrolled in the study. The patients were randomized to have 8 mg of Candesartan added in the first or second of two 12-week study periods. The primary end point was urine protein excretion, which was measured every 2 weeks for the 24-week period. Secondary end points included systolic and diastolic blood pressure, serum creatinine, urea and potassium levels. Candesartan was added against a background of standard care, which included other blood pressure lowering therapy.

Results. Lower urine protein excretion 2.4 vs 2.0 g in 24 h (P < 0.04, difference 0.45, CI 0.01, 0.9) and lower levels of systolic blood pressure 134 vs 128 mmHg (P < 0.001, difference 6.4, CI 3.2, 9.6) and diastolic blood pressure 82 vs 80 mmHg (P < 0.008, difference 2.7, CI 0.7, 4.6) were observed when Candesartan, 8 mg, was added to a regimen, which included an ACEI. No rise in serum creatinine occurred but there was a significant rise in urea, during the Candesartan arm of the study, from 12.3 to 13.8 mmol/l (P < 0.001). The addition of 8 mg of Candesartan in normotensive patients with chronic renal disease receiving ACEI appeared safe and was not accompanied by adverse effects apart from postural hypotension in three patients and a serum potassium level of 6.3 mmol/l in one.

Conclusions. In a private consulting practice setting, the addition of 8 mg of Candesartan in normotensive patients with chronic renal disease and proteinuria receiving an ACEI reduced proteinuria and blood pressure. The combination of Candesartan and ACEI appeared safe in this setting and may offer additional protection in preventing progression in chronic renal disease. Although the reduction of proteinuria was small (0.45 g/24 h) this reflected in part a lack of response in diabetic nephropathy and in part a marked rise in proteinuria after ceasing Candesartan in patients who did not complete the Candesartan arm of the study.

Keywords: angiotensin II receptor antagonist; angiotensin converting enzyme inhibitor; progressive chronic renal disease; proteinuria

Introduction

The renoprotective effect of angiotensin converting enzyme inhibitors (ACEI) is well established and they are now routinely used in chronic renal disease to reduce proteinuria and slow progression [1]. ACEI block angiotensin II generation by inhibiting the action of angiotensin converting enzyme, however, there is evidence that angiotensin II is generated by other pathways [1] and it is therefore possible that a combination of an ACEI together with an angiotensin receptor antagonist may provide a more complete blockade of the adverse effects of angiotensin II on proteinuria and blood pressure in patients with chronic renal disease.
The hypothesis for this study is that the addition of an angiotensin II receptor antagonist to a treatment regimen, which includes an ACEI, will further reduce proteinuria and blood pressure in patients with chronic renal disease.

**Subjects and methods**

This was an open randomized controlled crossover trial. Sixty adults, aged 23–75, were recruited from the private practices of three renal physicians in Melbourne. They were eligible for the study if they were currently taking an ACEI and had an unequivocal diagnosis of renal disease based on renal biopsy or diagnostic radiographic features. In addition they were required to have proteinuria of 0.5 g/24 h or above which had been stable for a period of 6 months or more. Blood pressures were well controlled at the time of entry. Patients were ineligible if their serum creatinine was above 350 μmol/l.

ACEI treatment was not altered on entry to the study because we planned to mimic as closely as possible the standard supervision and management of these patients in this private practice setting. Our hypothesis tested the value of addition of an angiotensin II receptor antagonist in this setting in patients stabilized for months or years on ACE inhibitor treatment. Table 1 shows the ACEI doses used in these patients. Forty-five patients were on what was considered maximum dose in the context of dosage in patients with impaired renal function. Lower doses were used in patients with lower blood pressures, several of whom were strictly normotensive when ACE inhibitor treatment was introduced for control of proteinuria. The dose was generally determined by the amount required to control hypertension.

Patients were randomly allocated to one of two groups in a 1 : 1 ratio. One group had Candesartan 8 mg daily added for the first 12 weeks after which Candesartan was ceased. The other group had Candesartan added in the second 12-week period after which it was ceased. Both groups remained on the usual ACEI regimen (Table 1) for the 24 weeks of the study. Because urine protein measurements vary without change in medication this was measured two weekly during the 24 weeks of the study. Frequency of patient visits was determined by clinical need but all attended at least every 12 weeks.

The primary end point of this study was the mean daily urine protein excretion in the six measurements available for each of the two study periods. Secondary end points included mean systolic and diastolic blood pressures, serum creatinine, urea and potassium measured at the end of each 12-week treatment period.

This study had an 80% power to detect a reduction in proteinuria of 0.7 g/day, with 25 individuals in each arm assuming a baseline proteinuria of 2.3 g/day (standard deviation 2 g/day) and no change in the non-Candesartan group. This data was derived from a similar group of patients studied over 6 months.

Patients were randomly assigned to the two groups using repeating blocks of 10 from a computer-generated random number list. After written informed consent had been obtained each physician phoned a central research assistant who assigned each patient according to the above list.

The average 24-h urine protein, blood pressure, urea, creatinine and potassium measurements during the three study periods were compared using a paired t-test or non-parametric equivalent. An intention to treat analysis was used. There were no defined stopping rules in the study. Ethical approval was provided by the Research and Ethics Committee of Epworth Hospital.

**Results**

All participants were enrolled over a period of 7 months. Sixty-five patients were approached. Five declined to enter the study, due to the inconvenience of frequent 24-h urine collections.

The renal diagnosis was reflux nephropathy (14), IgA glomerulonephritis (12), focal sclerosis (8), diabetic nephropathy (7), membranous glomerulonephritis (5), lupus nephritis (3), other glomerulonephritis (4) Alport’s syndrome (2) and other defined conditions (5).

The two randomized groups were well matched at entry for proteinuria, blood pressure and serum creatinine and urea levels (Table 2). Blood pressures were normal but urine protein, serum creatinine and urea were elevated (Table 2).

Two patients failed to attend but primary end points were available for analysis in 58 of 60 patients at the end of the two 12-week periods. Six patients did not complete their course of treatment in these two 12-week periods. Three developed postural hypotension and one developed hyperkalaemia (6.3 mmol/l) when Candesartan was added, one developed cholecystitis and one withdrew for personal reasons.

Table 3 shows a statistically significant reduction in 24 h proteinuria, and systolic and diastolic blood pressure, and a rise in serum urea in the Candesartan arm of the study. There was no change in mean serum creatinine or potassium levels.

Only one of seven patients with diabetic glomerulonephritis showed a reduction in proteinuria (Table 4), whereas 80% of non-diabetic patients showed reduced urine protein on the combination of ACEI and Candesartan. Blood pressure levels were higher during the study in diabetic patients (Table 4). Average blood pressure was 136/79 in diabetic patients compared with 128/80 in non-diabetic patients on ACEI and Candesartan. On ACEI, systolic blood pressure control was unsatisfactory in patients with diabetes with an average of 145/82 compared with 134/82 in non-diabetic patients.
proteinuria and blood pressure in chronic renal disease patients treated with angiotensin II receptor antagonist and ACEI

Table 2. Baseline characteristics of those randomized to the two intervention groups

<table>
<thead>
<tr>
<th></th>
<th>ACEI then ACEI + ARA group (n = 29)</th>
<th>ACEI + ARA then ACEI group (n = 31)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 24 h urinary protein (SD)</td>
<td>2.2 (1.7)</td>
<td>2.4 (2.4)</td>
<td>0.76</td>
</tr>
<tr>
<td>Mean systolic BP (SD)</td>
<td>134 (13)</td>
<td>139 (12)</td>
<td>0.15</td>
</tr>
<tr>
<td>Mean diastolic BP (SD)</td>
<td>84 (8)</td>
<td>82 (10)</td>
<td>0.36</td>
</tr>
<tr>
<td>Mean serum urea (mmol/l)</td>
<td>10.7 (7)</td>
<td>12.8 (8)</td>
<td>0.28</td>
</tr>
<tr>
<td>Mean serum creatinine (mmol) (SD)</td>
<td>1800 (20)</td>
<td>170 (10)</td>
<td>0.74</td>
</tr>
</tbody>
</table>

SD, standard deviation; ACEI, angiotensin converting enzyme inhibitor; ARA, angiotensin receptor antagonist.

Table 3. Outcomes during the ACEI alone and ACEI plus ARA periods

<table>
<thead>
<tr>
<th></th>
<th>ACEI only period</th>
<th>ACEI + ARA period</th>
<th>P value</th>
<th>Difference (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean 24 h urinary protein (SD) (n = 58)</td>
<td>2.4 (2.7)</td>
<td>2.0 (2.2)</td>
<td>&lt;0.04†</td>
<td>0.45 (0.01, 0.9)</td>
</tr>
<tr>
<td>Mean systolic BP (SD) (n = 54)</td>
<td>134 (13)</td>
<td>128 (13)</td>
<td>&lt;0.001</td>
<td>6.4 (3.1, 9.6)</td>
</tr>
<tr>
<td>Mean diastolic BP (SD) (n = 54)</td>
<td>82 (8)</td>
<td>80 (7)</td>
<td>0.008</td>
<td>2.7 (0.7, 4.6)</td>
</tr>
<tr>
<td>Mean serum potassium mmol/l (n = 53)</td>
<td>4.7 (0.7)</td>
<td>4.7 (0.6)</td>
<td>0.88</td>
<td>0.01 (–0.2, 0.2)</td>
</tr>
<tr>
<td>Mean serum urea mmol/l (n = 53)</td>
<td>12.3 (7.5)</td>
<td>13.8 (8.5)</td>
<td>&lt;0.001</td>
<td>−1.5 (−2.2, −0.7)</td>
</tr>
<tr>
<td>Mean serum creatinine mmol/l (SD) (n = 53)</td>
<td>160 (0.2)</td>
<td>170 (0.1)</td>
<td>0.31</td>
<td>−0.01 (−0.01, −0.001)</td>
</tr>
</tbody>
</table>

†Difference between ACEI only period and ACEI and ARA period (paired t-test); ††P value was <0.001 using non-parametric t-test equivalent. CI, confidence interval; SD, standard deviation; ACEI, angiotensin converting enzyme inhibitor; ARA, angiotensin II receptor antagonist.

Table 4. Proteinuria and blood pressure in seven subjects with diabetic nephropathy

<table>
<thead>
<tr>
<th></th>
<th>Urine protein g/24 h</th>
<th>Blood pressure</th>
<th>Urine protein g/24 h</th>
<th>Blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAB</td>
<td>1.1</td>
<td>135/85</td>
<td>1.1</td>
<td>155/89</td>
</tr>
<tr>
<td>MAN</td>
<td>2.1</td>
<td>130/78</td>
<td>2.3</td>
<td>150/80</td>
</tr>
<tr>
<td>SCR</td>
<td>0.6*</td>
<td>120/71</td>
<td>1.2</td>
<td>150/85</td>
</tr>
<tr>
<td>CRI</td>
<td>0.7</td>
<td>140/82</td>
<td>0.7</td>
<td>140/80</td>
</tr>
<tr>
<td>KUM</td>
<td>1.9</td>
<td>130/80</td>
<td>1.6</td>
<td>130/90</td>
</tr>
<tr>
<td>DEC</td>
<td>4.9</td>
<td>150/80</td>
<td>4.9</td>
<td>140/80</td>
</tr>
<tr>
<td>CAO</td>
<td>1.7</td>
<td>144/79</td>
<td>1.9</td>
<td>151/67</td>
</tr>
<tr>
<td>MEAN</td>
<td>1.86</td>
<td>136/79</td>
<td>1.96</td>
<td>145/82</td>
</tr>
</tbody>
</table>

*Significant fall in urine protein on combined ACEI and ARA. ARA, angiotensin II receptor antagonist; ACEI, angiotensin converting enzyme inhibitor.

Discussion

This study demonstrated a statistically significant reduction in proteinuria and in systolic and diastolic blood pressure when Candesartan was added to a regimen, which included an ACE inhibitor that was judged to be at the maximum recommended dose in most patients. It is standard practice to treat patients with chronic renal disease with an angiotensin converting enzyme inhibitor for control of proteinuria and blood pressure and to delay progression [1]. Evidence on prevention of progression in chronic renal disease with angiotensin II receptor antagonists is less secure but two recent studies in type II diabetes show unequivocal prevention of progression using Irbesartan [2] and Losartan [3]. The patients in these two studies were not receiving ACE inhibitors and as expected proteinuria was reduced by the angiotensin II receptor antagonists. In a separate study in the same journal Parving’s group demonstrated that Irbesartan delayed onset of proteinuria in Type 2 diabetes [4].

Because reduction of blood pressure and reduction of urine protein levels independently decrease the rate of decline of renal function [1,5] our results suggest that the combination of an ACE inhibitor and an angiotensin II receptor antagonist may be more effective than an ACE inhibitor alone in delaying progression.

Since our study was completed a publication has reported results which differ from ours showing no fall in either blood pressure or urine protein level when Losartan, 50 mg, was added to Lisinopril, 40 mg, in 16 patients with proteinuria and moderately advanced chronic renal failure [6]. There are many differences between the patients in Agarwal’s study and in ours. Mean blood pressures in his study were much higher at entry (156/88 compared with 139/83). Seventy-five per cent of patients studied by Agarwal had diabetes compared with 11% of our patients. Our patients with diabetes had higher blood pressures in both treatment arms than our whole group (Table 4). We did not demonstrate reduction in proteinuria in six of seven patients with diabetes perhaps because of higher blood pressure levels. The patient in whom urine protein halved showed a much better systolic and diastolic blood pressure response to addition of Candesartan than the other six patients (Table 4).
In the REIN study, Ruggenenti et al. [7] have reported that higher blood pressures at entry are associated with higher blood pressures on Ramipril and less reduction in proteinuria and these features were seen in his patients with diabetes who also progressed much more rapidly than non-diabetic patients. This different response in diabetes may help to explain our own findings in diabetic nephropathy as well as the lack of reduction in proteinuria in patients in Agarwal’s study, 75% of whom were diabetics.

Eighty per cent of our non-diabetic patients had lower urine protein levels during the ACE inhibitor plus Candesartan phase. Most patients who failed to respond were obese which is of interest in view of the very high mean BMI level in Agarwal’s patients. The obese patients who failed to respond in our study could well fit into the hyperinsulinaemia/hyperlipidaemia syndrome and as Agarwal also found no response in obese subjects it is possible that there is an association between this syndrome and lack of response as appears to be the case in diabetes. We are currently reviewing the relationship between BMI and urine protein fall on ACEI and angiotensin II receptor antagonists.

A major difference between Agarwal’s study and ours is the use of 50 mg of Losartan in his study and 8 mg of Candesartan in ours. We cannot find a direct comparison of these drugs but our experience with 50 mg of Losartan suggests that both the anti-hypertensive effect and anti-proteinuric effects are less than those seen with 8 mg of Candesartan. The fact that blood pressures did not fall in Agarwal’s study whereas we found a highly significant fall in both systolic and diastolic blood pressure supports this view, although the questions relating to diabetes and blood pressure confound the issue.

The majority of Agarwal’s patients were black (10/16). There is evidence that the response of left ventricular hypertrophy to ACE inhibition is reduced in blacks [8] and perhaps they also differ from caucasians in other responses to drugs that inhibit the renin–angiotensin system. A recent publication did, however, show that an ACEI slowed progression in hypertensive nephrosclerosis [9]. Our sixty patients included 55 caucasians and five Asians and these racial differences could contribute to the different response in urine protein and blood pressure in the two studies.

An important difference was the design of the study. Our treatment periods were 12 weeks; Agarwal’s were 4 weeks. We measured urine protein six times in each 12-week period. Agarwal measured protein at the beginning and end of 4-week period. Our frequent urine protein levels were included because of the known spontaneous variations in urine protein levels. Some patients in whom impressive reduction of urine protein was observed showed a progressive fall over the 12-week period. For example a patient with Alport’s syndrome with heavy proteinuria for 24 years showed a progressive fall from 8.7 g in 24 hours after the first 2 weeks of combined ACEI and Candesartan to 2.0 g in 24 h at the end of 12 weeks. His urine protein remains at 2.2 g in 24 h 2 years later on combined ACE inhibitor and Candesartan treatment. A second patient with advanced reflux nephropathy and about 1 g in 24 h of proteinuria for 6 years prior to the trial showed a progressive fall from 0.59 g in 24 h after 2 weeks of Candesartan, to 0.19 g in 24 h after 12 weeks on combined ACE inhibitor and Candesartan. A year after the trial was completed she continues on combined treatment and has no proteinuria (0.09 g in 24 h). In these and other patients progressive falls in urine protein were observed with treatment for longer than 12 weeks and 20% of patients in this study have no proteinuria after 6–9 months of combined ACE inhibitor and Candesartan [10].

The mean fall in urine protein that we recorded was quite small (0.45 g in 24 h) partly due to the fact that when the protocol was written, we had not anticipated the progressive fall and therefore the protocol included an analysis of the mean of all six protein levels over the 3-month period. Diabetic patients in whom urine protein did not fall and the patients who did not complete the Candesartan arm of the study also contributed to the low mean fall in urine protein. The urine protein rose in all patients in whom Candesartan was stopped, the most marked rise was from 1.7 to 12.7 g per 24 h. If we analysed only those who completed the course of ACE inhibitor and Candesartan, the mean fall was 0.65 g (27%).

We found only one other published randomized study of the effect of an ACEI combined with an angiotensin receptor antagonist in chronic renal disease. This was designed to test tolerability and safety of a combination of Valsartan and Benazepril [11]. The authors cautioned about interpretation of their data on protein/creatinine ratios because they were derived from pooled data from patients who may or may not have had either proteinuria or hypertension. Their study in progressive chronic renal failure showed a significant rise in creatinine levels on the combination of Valsartan and Benazepril. Creatinine levels did not rise significantly in our trial, however, we found that the urea was slightly elevated during the ACEI plus Candesartan phase. We would caution, however, that our previous unpublished experience in individual patients has shown an irreversible deterioration in renal function in occasional patients with serum creatinine levels above 350 μmol/l, when an ACEI and angiotensin receptor antagonist are combined.

Hyperkalaemia on combined therapy was less of a problem than anticipated which confirmed Ruilope’s finding [11]. We withdrew only one patient because of hyperkalaemia.

There are two additional small non-randomized studies of the effect of adding Losartan in patients receiving an ACEI, one in eight patients with IgA glomerulonephritis [12] and another in 11 patients with various chronic renal diseases [13]. Both studies showed a reduction in proteinuria when Losartan was added to ACEI treatment. Mogensen et al. [14] reported that a combination of Candesartan and Lisinopril reduced microalbuminuria in diabetic patients more than either drug alone.
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It is often argued that the results of large multicentre trials conducted in specialist centres may not predict or reflect what will occur in standard medical practice. This study was designed specifically to test our hypothesis in the setting of ‘standard medical practice’ and based on the intervals at which patient’s blood pressures and biochemical indices are normally measured. A high percentage of the patients approached agreed to participate. We did not change their ACEI inhibitor or other medications at entry because we wished the study to reflect the addition of an angiotensin II receptor antagonist in this setting.

The design of our trial did not permit us to determine whether blood pressure reduction accounted for the reduction in proteinuria but as both are of proven benefit in the prevention of progression [1,5], we believe our results have important implications for standard clinical practice in patients with chronic renal disease.

The only cost incurred above that of usual management was the cost of two weekly urine protein estimations. Hostetter [13] comments on the considerable cost of studies such as those recently reported in Type 2 diabetes [2,3]. Such major trials can only be funded by the pharmaceutical industry and the protocol is often dictated by industry and as Hostetter states ‘trial design blurs into marketing strategy’. It is very legitimate to ask why an ACE inhibitor arm was not included in these studies in Type 2 diabetes [2,3] or why an angiotensin II receptor antagonist was not added to ACEI treatment that many patients were presumably receiving prior to the trial. We now may never know if ACE inhibitors are of value in Type 2 diabetes as was suggested by the earlier study by Ravid [15]. An investigator-initiated study would almost certainly have asked this question.

Hostetter [13] also calls for re-examination of the use of surrogate markers like proteinuria as a valid marker of progression. Ruggenenti et al. [7] observe that in the REIN study long-term protection from decline in renal function correlates with short-term reduction in proteinuria, which supports the concept of using proteinuria as a surrogate marker of progression as we did.

Our study demonstrates the safety in a private practice setting of adding an angiotensin receptor antagonist to a regimen that includes an ACEI in patients with modest impairment of renal function and well-controlled blood pressure levels. It also demonstrates a significant reduction in urine protein, and in both systolic and diastolic blood pressure levels which independently slow the rate of decline of renal function [1,5]. Combined ACEI and angiotensin II receptor antagonists may thus prove in larger studies to delay progression of renal disease.

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