

Long-term safety of high-dose angiotensin receptor blocker therapy in hypertensive patients with chronic kidney disease

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Background Reducing urinary protein excretion in patients with renal disease is an important therapeutic target to prevent the progression of renal and cardiovascular disease. Drugs such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ARBs), which block the actions of the renin–angiotensin–aldosterone system, are recommended because they reduce blood pressure and proteinuria. Recently, the use of higher doses of ARBs, up to three times the maximal approved dose, resulted in further reductions in protein excretion. Despite the effectiveness of this therapeutic approach, no long-term safety analysis has been conducted in patients receiving high-dose ARB treatment.

Objective To study the long-term safety of high-dose ARB treatment.

Methods We observed 48 patients [44 men and 4 women; ages 64 ± 15 years (mean \pm SD), weight 88 ± 28 g, estimated glomerular filtration rate 53 ± 23 ml/min] receiving treatment with high doses (1.5–5 times greater than the maximum approved dose) of ARBs, for 40 ± 24 months (range 3–98 months).

Results The average ARB dose tended to increase over time and was 3.2 ± 1.2 times greater at the end of the study than that at the start. Systolic blood pressure was similar at the beginning and end of the study period (132 ± 20 mmHg and 125 ± 20 mmHg, respectively), but diastolic blood pressure showed a decrease throughout the study and was significantly reduced ($P < 0.05$) in association with 1.5 \times and 2 \times the maximum ARB dose (73 ± 11 mmHg and 72 ± 10 mmHg, respectively) when compared with baseline (78 ± 11 mmHg). There was a trend ($P > 0.05$) for increases

in concentrations of serum potassium (0.2 ± 0.9 mmol/l) and creatinine (0.3 ± 0.7 mg/dl) with increases in dose from baseline to the end of the study. Serum creatinine concentration was greater ($P < 0.05$) at the periods of 3 \times and 4 \times the maximum dose, but this represented increases of only 12% and 20% from baseline, respectively.

Conclusions High-dose ARB treatment in patients with chronic renal disease is not associated with any clinically significant long-term negative effects on serum creatinine or potassium and is thus a important therapeutic modality with which to achieve further reductions in urinary protein excretion. *J Hypertens* 24 (suppl 1):S00–S00 © 2006 Lippincott Williams & Wilkins.

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Introduction

Evidence is mounting that proteinuria is an independent predictor of outcomes in patients with renal or cardiovascular disease, or both [1–3]. Blockade of the renin–angiotensin–aldosterone system results in additional reductions in urinary protein excretion beyond its blood pressure-decreasing effect [4,5]. The reduction in proteinuria, using angiotensin receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEIs), or both, is then an important therapeutic strategy with which to achieve further reductions in the frequency of cardiovascular and renal events [6,7].

Blocking the renin–angiotensin–aldosterone system using ACEIs or ARBs at doses greater than those required to reduce blood pressure may be an effective strategy with which to reduce proteinuria independent of blood pressure while also preserving renal function [8,9]. However, the optimal doses of ARBs or ACEIs for the reduction of proteinuria in patients with chronic kidney disease has not been determined [10]. Moreover, it is apparent that the doses of ACEIs and ARBs that have been approved for use were based on their efficacy in decreasing blood pressure, and may not be adequate for determining the optimal dose to reduce proteinuria. We

first demonstrated that the use of high-dose candesartan cilexetil, up to 96 mg/day [three times (3×) the maximal dose], resulted in a dose-dependent reduction in proteinuria [8].

Recently, a short-term safety study using 5× the maximum approved dose of candesartan cilexetil (160 mg/day), administered for 8 weeks, was not associated with increases in serum creatinine or potassium concentrations [11]. The purpose of this clinical observational trial was to examine the long-term (average evaluation period 3.4 years) safety effects of high-dose ARB treatment, determination of which will allow investigators to evaluate the efficacy of these agents for the further reduction of proteinuria.

Methods

Patients

In this investigation, patients with chronic renal disease from a clinical practice setting were observed, retrospectively, during long-term high-dose ARB treatment. The patient population was heterogeneous, with various renal diseases (diabetic and non-diabetic). Criteria for the patients' entry to the study included increased urinary spot microalbuminuria (at least 30 mg albumin/g creatinine per day), or 24-h urinary protein excretion of at least 300 mg/day. Exclusion criteria included intermittent normal protein excretion at 1× the maximum recommended ARB dose, pregnancy, history of angioedema, allergy to ARBs, or a history of rapidly progressive renal failure.

Patients were permitted to have been treated with any antihypertensive medications, including ACEIs. At baseline, patients received ARBs in the usual doses approved by the USA Food & Drug Administration (FDA) for blood pressure reduction. There was no washout period of ARBs or ACEIs. Data analysis was performed only for patients who were treated with high-dose ARBs for a minimum of 6 months.

Design

All patients received at least 1.5× the maximum recommended dose of ARBs, which were titrated in order to obtain a further reduction in proteinuria, while not exceeding 5× the FDA-recommended dose. Doses were increased by 0.5–1.0× the maximal dose of ARBs in equivalents at varying intervals depending upon the patient's individual visit schedule. For patients not achieving normal protein excretion, the ARBs were increased until 5× the maximal recommended dose was administered. Once a patient had normalized their urinary protein excretion, that dose of ARB was maintained, and the patient was monitored.

Patients were withdrawn from the trial if their serum potassium concentration was 6 mmol/l or more on two

simultaneous occasions, they required renal replacement, they had a hypersensitivity reaction (e.g. angioedema) to high-dose ARB therapy, or they were non-compliant with the study medication. They were required to take their medication at the same time in the morning each day.

Measures

Study parameters evaluated included systolic blood pressure (SBP), diastolic blood pressure (DBP), serum creatinine and serum potassium. An estimated glomerular filtration rate (GFR) was calculated for each patient [12]. All patients received dietary counseling in the event that their serum potassium concentration was 5.5 mmol/l or more. Any individual with a serum potassium concentration of 6.0 mmol/l or more underwent a repeat measurement within 5 days.

Statistical analysis

Data were analyzed from all patients treated with up to 1–5× the FDA maximal recommended dose of ARBs for more than 6 months. To enable comparisons between patients receiving different ARBs, all doses were recorded as equivalent multiples of doses (1–5× equivalents). Because of the nature of trial in a clinical practice setting and the small sample size involved, the use of conventional parametric methods for data analysis was precluded and, thus, minimal statistics without extensive adjustments were used. Because of the small and uneven sample size, the variable duration of dosing intervals, and incomplete laboratory data at various dosing periods, an unpaired *t*-test was performed to test for differences. The means of the main variables of interest at each level of ARB dosing in the range 1.5–5× the maximally recommended dose were compared with the baseline, to assess for significant variance. Multiples of the maximal ARB dose (i.e. 1.5–5×) were used in order to compare the safety of treatment by dose of different ARBs administered, rather than by total duration of treatment. The maximal FDA-recommended dose for each ARB was considered to be one equivalent. Significance was defined as $P < 0.05$. All statistics were performed using SAS software (version 8.1, SAS Institute, Cary, North Carolina, USA) and all values are reported as mean \pm SD.

Table 1 Baseline physical characteristics of 48 patients evaluated on high-dose angiotensin II receptor blockers (ARBs) for a period of 40.3 \pm 24 months

Characteristic	Value
Sex (M/F)	44/4
Age (years)	64 \pm 15
Body weight (kg)	87.7 \pm 28
GFR (ml/min)	52 \pm 23
24-h urinary protein excretion (g)	2.26 \pm 2.4
End of study maximal dose ^a	3.2 \pm 1.2 \times ARB _{max}

Values are number or mean \pm SD. GFR, glomerular filtration rate (estimated value).
^aReported in multiples beyond the USA Food & Drug Administration approved maximum doses for ARBs.

Table 2 Clinical blood pressure and plasma electrolyte data at baseline and after increasing dosage of the angiotensin II receptor blocker (ARB; reported in multiples beyond the USA Food & Drug Administration approved maximum dose)

	ARB dose					
	1×	1.5×	2×	3×	4×	5×
<i>n</i>	48	22	43	33	21	10
SBP (mmHg)	133 ± 20	129 ± 13	130 ± 18	129 ± ± 17	125 ± 16	123 ± 18
DBP (mmHg)	78 ± 11	73 ± 11*	72 ± 10*	74 ± 10	73 ± 11	74 ± 9
Serum creatinine (mg/dl)	1.7 ± 0.8	1.7 ± 1.0	1.9 ± 1.0	2.0 ± 0.9*	2.1 ± 0.8*	2.7 ± 1.1
Serum potassium (mmol/l)	4.5 ± 0.4	4.5 ± 0.5	4.7 ± 0.6	4.7 ± 0.6	4.8 ± 0.6*	5.0 ± 0.9
24-h urinary protein excretion (g)	2.4 ± 2.4	2.2 ± 2.7	2.2 ± 2.0	2.2 ± 3.3	2.3 ± 2.6	3.1 ± 2.9
Duration (months)		17 ± 14	9.5 ± 12	11 ± 10	9 ± 5	11 ± 5

Values are mean ± SD. *n*, number of patients; SBP, DBP, systolic and diastolic blood pressures. **P* < 0.05 compared with baseline.

Results

Forty-eight patients were followed for 40 ± 24 months (range 3–98 months) of treatment. The background status of the patients is shown in Table 1, including age, estimated GFR, 24-h urinary protein excretion, duration of treatment, and average dose at the end of the study. Most patients in this study (*n* = 34) were administered candesartan cilexetil; valsartan (*n* = 6), losartan (*n* = 6), irbesartan (*n* = 3) and olmesartan (*n* = 2) were also used. The mean age was 64 ± 15 years, years, and most of the patients (*n* = 44; 92%) were men. Patients had both diabetic and non-diabetic renal diseases. Hypertensive individuals were taking other antihypertensive medications including calcium channel blockers, diuretics, ACEIs, vasodilators, and β-blockers. Table 2 summarizes the number of patients with data recorded at each study period and the average duration of treatment at each period.

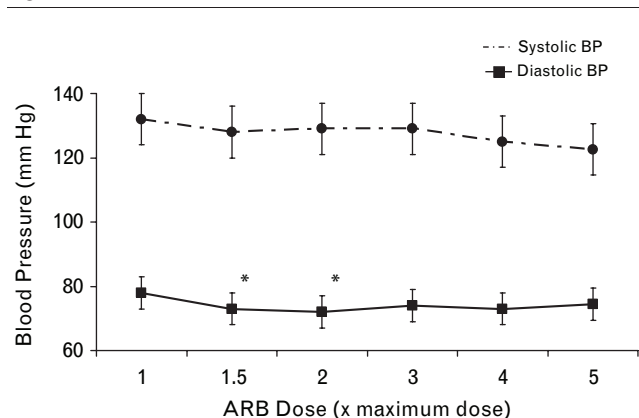
Table 2 also presents an evaluation of the effect of increasing doses of ARBs from baseline (1×) to 5× equivalence doses. The mean SBP at baseline was

132 ± 20 mmHg and the mean DBP was 78 ± 11 mmHg. SBP was reduced by from 3 to 9 mmHg during the various periods of high-dose ARB, but was never statistically different from baseline. The DBP decreased from baseline by from 4 to 6 mmHg throughout the period of high-dose ARB administration; this was significant at 1.5× and 2× the maximum dose (Fig. 1).

The baseline serum creatinine and serum potassium concentrations were 1.7 ± 0.8 mg/dl and 4.5 ± 0.4 mmol/l, respectively. The serum creatinine concentration increased slightly with increases in dose and was significant (*P* < 0.05) at the periods of 3× (2.0 ± 0.9 mg/dl) and 4× (2.1 ± 0.8 mg/dl) doses, representing increases, above baseline, of 12% and 20%, respectively (Table 2). During the trial, at various study periods, four patients exhibited an increase in serum creatinine concentration greater than 50% from baseline. Of the 12 patients who had serum creatinine concentrations of 2.0 mg/dl or more at baseline, five exhibited a reduction, and the other seven had an increase of only 18% above baseline (Fig. 2).

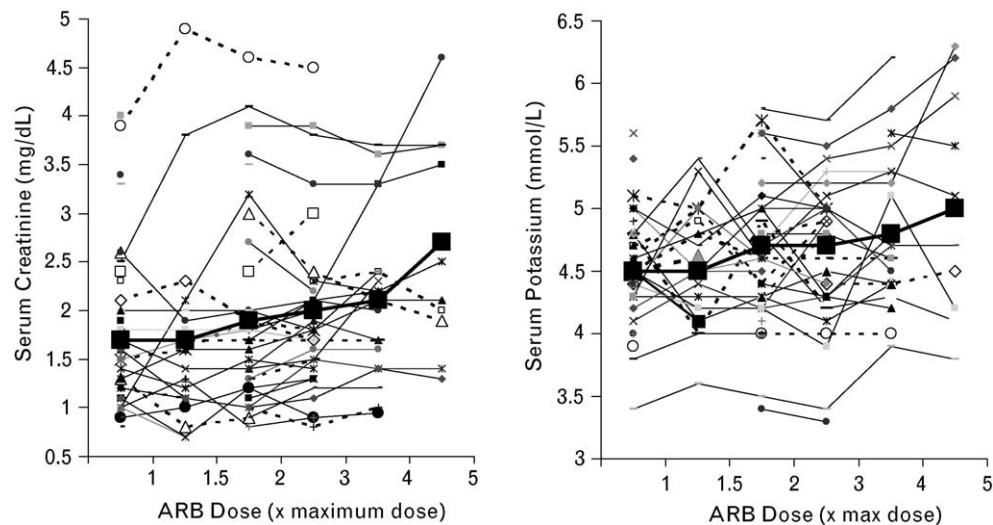
There was a trend for the serum potassium concentration to increase during the study periods, but it was significantly increased compared with baseline only at the 4× dose (4.8 ± 0.6 mmol/l compared with 4.5 ± 0.4 mmol/l) (Table 2). During the study, the serum potassium concentration increased to more than 5.5 mmol/l in six patients. The increase was to more than 6.0 mmol/l in two of these patients, but in these individuals the concentration decreased to less than 6 mmol/l within 5 days after the dose was reduced.

The baseline urinary protein excretion of the patients is presented in Table 1. Although there was a trend for urinary protein excretion to be reduced during the study, there was no significant change (*P* > 0.05), probably related to the incomplete data set, as many patients did not provide a 24-h urine collection sample at various dosing periods (only 18 of the 48 gave a sample at the 4× dose, and only nine at the 5× dose period) (Table 2).

Fig. 1

Effect of high-dose angiotensin II receptor blocker (ARB) treatment (from 1× to 5× the recommended dose) on systolic (●) and diastolic (■) blood pressures. Values are mean ± SD. **P* < 0.05 compared with baseline in 48 patients.

Fig. 2



Individual serum potassium and serum creatinine responses in patients given from 1× to 5× the maximal recommended doses of angiotensin receptor blockers (ARBs). Colored lines represent paired values for each individual at differing equivalents (from 1× to 5×) of ARBs administered. Mean values of each equivalent ARB dose are shown as the bold black line.

There were no serious adverse events related to drug or dose during the course of the study. In addition, there were no serious hyperkalemic events or episodes of acute renal failure. One patient had a severe transplant rejection and went on to recommence hemodialysis. Two patients experienced slow but steady progressive renal failure as a result of glomerular disease, requiring renal replacement treatment after a mean of 50 months. Lastly, two individuals died from non-renal causes during the duration of the investigation.

Discussion

The findings of this investigation demonstrate that ARBs, in doses higher than those approved by the FDA, are safe and well tolerated when given for periods of up to 98 months in patients with chronic kidney diseases. This study was a follow-up to our 8-week pilot study of candesartan cilexetil 160 mg/day administered for 2 months to patients with chronic kidney disease and overt nephropathy [11]. Both our short-term (8 week) and this current long-term (3–98 months; mean 40 ± 24 months) evaluation of high-dose ARBs were not associated with any serious adverse effects. Transient hyperkalemia and azotemia, without significant renal failure, were observed during the period of highest dosage. Using ARBs at doses beyond their maximal antihypertensive dose as a therapeutic strategy to achieve further reductions in proteinuria when patients have their blood pressure optimally controlled may be warranted on the basis of the safety results observed in this trial. This is an important finding, because the degree of proteinuria is an independent risk factor in the development of renal

and cardiovascular disease and reducing it may be disease-preventive [3].

This is the first study to examine the effect of high-dose ARB treatment on long-term safety. However, there have been previous studies, primarily in patients with cardiac disease, which have examined the use of combined ACEI and ARB treatment (a form of maximal renin–angiotensin–aldosterone system blockade), that have reported safety findings similar to those observed in the present study, in relation to changes in serum creatinine and serum potassium concentrations. In the Valsartan Heart Failure Trial [13] and Randomized Evaluation of Strategies of Left Ventricular Dysfunction study [14], increases in serum potassium concentration of 0.12 mmol/l and serum creatinine concentration of 0–0.2 mg/dl were reported. In the more recent Candesartan in Heart Failure – Assessment of Reduction in Mortality and Morbidity (CHARM)-Added heart failure study [15], a slightly greater number of patients in the ACEI + ARB arm (3%, compared with 1% in the control arm) were reported to have serum potassium concentrations of 6 mmol/l or more. In addition, there were greater rates of withdrawal because of renal dysfunction and hyperkalemia in the ACEI + ARB group (11.3%, compared with 4.8% in the control arm), indicating a need to monitor renal function and serum potassium in patients undergoing maximal blockade of the renin–angiotensin–aldosterone system.

Short-term studies in patients receiving high-dose ARB therapy have also revealed effects on serum creatinine

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and serum potassium concentrations similar to those reported in our trial. In a recent study, Rossing *et al.* [9] reported a significant increase (0.3 mmol/l) in baseline serum potassium concentration during treatment with normal and high-dose irbesartan (600 mg); in patients receiving irbesartan 900 mg, the concentration increased no more than 0.4 mmol/l. The investigators did not therefore report the increase in serum potassium concentration as dose dependent. Preliminary reports from the two only other studies examining high-dose ARB treatment in patients with proteinuria and renal disease have not reported any safety concerns [16,17].

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Currently, there are two trials examining the efficacy of high-dose ARB treatment in reducing proteinuria in patients with renal disease. The first, the Super Maximal Atacand Renal Trial (SMART), was designed to determine the optimal dose for candesartan cilexetil (up to 128 mg/day) for maximum reduction of proteinuria [18]. The second, the Diovan Reduction of Proteinuria Study (DROP), is investigating the use of valsartan, up to 640 mg/day, in patients with type 2 diabetes. Both trials are expected to report in 2006.

Conclusions

This long-term safety trial demonstrated no clinically significant or persistent changes in serum creatinine or serum potassium concentrations in patients studied over periods of from 3 to 98 months while receiving various ARBs at high doses (1.5–5× the maximum recommended FDA-approved dose). We conclude that high-dose ARB treatment in patients with hypertension and renal disease is not associated with any long-term adverse effects and is thus an important therapeutic approach to further reductions in proteinuria. However, periodic measurement of changes in serum creatinine and serum potassium concentrations is still warranted in patients undergoing high-dose ARB therapy, as there is a potential for an increase in the risk of hyperkalemia and renal impairment, particularly when ARBs are used in conjunction with aldosterone receptor antagonists (e.g. spironolactone, eplerenone) or non-steroidal anti-inflammatory drugs [15,19]. On the basis of the findings in this analysis, high-dose ARB therapy remains a viable option for the further reduction of proteinuria in patients with chronic kidney disease. Results from two multicenter studies currently in progress are needed to define further the potential benefits and side-effects associated with high-dose ARB therapy.

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