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Safety and Tolerability of High-Dose Angiotensin Receptor Blocker Therapy in Patients with Chronic Kidney Disease: A Pilot Study

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Key Words

Angiotensin-receptor blockers · Candesartan · Chronic renal disease · Diabetic renal disease · Non-diabetic renal disease · Renoprotection · Supramaximal doses

Abstract

Background: The progression of renal disease is ameliorated by drugs that inhibit the renin-angiotensin system (RAS). The doses used to slow the progression of renal disease may not completely suppress the RAS for 24 h and may explain why some patients do not obtain optimal renoprotective benefits from therapy. This pilot study was initiated to determine the safety and tolerability of using higher doses, than currently approved by the Food and Drug Administration, for the angiotensin-receptor blocker (ARB) candesartan cilexetil in patients with chronic kidney disease. We hypothesized that higher doses will be safe and well tolerated. Consequently, this should be a viable strategy for larger clinical trials evaluating the preservation of renal function. ***Methods:*** Twelve patients (10 males; age = 57 ± 14 years) with a history of diabetic or non-diabetic chronic kidney disease were enrolled in an 8-week open-label trial. Patients received candesartan titrated to a targeted dosage of 160 mg/day (5 times above the currently approved maximum dose) and remained at that dosage for the subsequent 4 weeks. The safety and tolerability of the higher doses were determined by measures of blood pressure, serum creatinine and potassium. ***Results:*** Candesartan was well tolerated with no serious drug-related adverse events reported. Serum creatinine concentrations throughout the study were not different ($p > 0.05$) from baseline levels (2.0 ± 0.5 mg/dl). Plasma potassium concentrations at 160 mg/day candesartan (4.9 ± 0.7 mEq/l) were similar ($p > 0.05$) to those at baseline (4.8 ± 0.5 mEq/l). ***Conclusions:*** The results of this pilot study suggest that supramaximal doses of ARBs are safe and well tolerated in patients with chronic kidney disease, while reducing both blood pressure and proteinuria. This study demonstrates the need to further investigate the optimal dosing strategy for ARBs in reducing the progression of renal disease.

Introduction

Although elevated blood pressure (BP) is a significant risk factor for the development and progression of renal dysfunction, renal disease can still progress to end-stage renal disease despite aggressive BP control [1]. Moreover,

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based on evidence demonstrating that residual proteinuria is an independent risk factor for the progression of renal disease, renoprotective strategies currently focus on the reduction of proteinuria in addition to BP control [2]. Agents such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) that block circulating and intra-renal components of the renin-angiotensin system (RAS) decrease proteinuria and have been identified as being among the most important therapeutic strategies to limit the progression of chronic renal disease [3, 4].

Blockade of the RAS is associated with a renoprotective effect that is partially independent of BP lowering [5]. However, the optimal doses of ACE inhibitors and ARBs to prevent the progression of renal disease have not been identified. The currently used doses of these agents are based on their BP-lowering effects [6]. In order to effectively block the RAS, doses greater than those needed for BP lowering may be required. Indeed, several studies have demonstrated that using higher doses of ACE inhibitors, ARBs or combinations of these agents improves their renoprotective properties, independent of further reductions in BP [7–9]. Thus, the dose-response curve for renoprotection may not be the same as it is for hypertension [2]. Utilizing a renoprotective strategy that titrates the ACE inhibitor or ARB dose to the decrease in proteinuria may be warranted but is not practical until more safety and tolerability data are available using higher doses than are currently approved.

Using supramaximal doses of ACE inhibitors is of particular concern to many physicians because of the serious adverse effects previously associated with using captopril at high dosages (>300 mg/day). In contrast, ARBs are known to be very well tolerated and have no added concerns for dose-related increases in serum creatinine or hyperkalemia incidence [10]. Furthermore, ARBs can theoretically provide a more complete blockade of the RAS because of their ability to block the angiotensin II type-1 receptor regardless of whether angiotensin II is generated through ACEI or non-ACEI pathways. Preliminary observations in our clinic have demonstrated that the ARB, candesartan cilexetil (approved dosage range, 8–32 mg/day), was well tolerated at doses up to 96 mg/day and seemed to result in dose-related reductions in urinary protein excretion [11]. The objective of this pilot study was to examine the safety and tolerability of higher dosages of candesartan (up to 160 mg/day) in patients with proteinuria and chronic kidney disease to determine the viability of conducting a larger dose-response clinical trial.

Methods

Subjects

Entry criteria included patients with a history of chronic kidney disease (proteinuria >500 mg/day). Adult males and females (not pregnant or lactating) who were ARB-naïve and not hypersensitive to or intolerant of ACE inhibitors were included in the study. Our objective in enrolling ARB-naïve patients was to prevent any beneficial effects of previously administered ARBs from influencing the results of this study. Patients who were receiving background ACE inhibitor therapy were required to undergo a 4-week washout phase prior to study initiation.

Twelve patients were selected for participation in the study. There were no baseline BP requirements for study entry. Patients with known or suspected causes of the following were excluded: secondary hypertension (e.g., renovascular stenosis, primary hyperaldosteronism); history of transient ischemic attacks, cerebrovascular accidents, or hypertensive encephalopathy; significant cardiac disease; or a history of autoimmune disease, idiopathic angioedema, collagen vascular disease or Gilbert's disease. The following also were exclusion criteria: a history of malignancy, seizure disorder, psychiatric disorder, alcohol or drug abuse, or HIV infection; a serum creatinine level of >3.0 mg/dl, or hepatic transaminase levels of >3 times the upper limits of normal. Nephrotic syndrome was not an exclusion criterion.

All patients provided written informed consent prior to inclusion in the study. The study was approved and monitored by the Western Institutional Review Board and an Investigational New Drug number was obtained from the Food and Drug Administration for the study.

Design

In order to test the hypothesis that higher doses of candesartan are safe and well tolerated, we utilized an 8-week, open-label dose-escalating trial of candesartan initiated at 16 mg/day, increasing to 64 mg/day after week 2 and to 160 mg/day after week 4. Patients were maintained at the 160 mg/day dosage for the final 4 weeks of the study. Patients were instructed to take the study medication in the morning at the same time each day. Tablet counts were performed at each visit to assess treatment compliance.

Assessments

Assessments included physical examination (weeks 0, 1, 2, 4, 6, 8) and clinical chemistry/hematology (weeks 0, 1, 2, 4, 6, 8). Twenty-four-hour urine collections were conducted at baseline and at weeks 4 and 8. Plasma (morning collection, 22–26 h post-dose) and urine samples for determining candesartan concentrations were also obtained after weeks 4 and 8. To test the hypothesis that higher doses of candesartan were safe, serum measurements of potassium (K^+) and creatinine were conducted at weeks 0, 1, 2, 4, 6, 8. Urinary sodium, K^+ and creatinine levels were measured at weeks 0, 4, 8 from the collected 24-hour urine sample. Trough, sitting BP measurements were obtained at baseline and at weeks 0, 1, 2, 4, 6, 8. Plasma and urine candesartan concentrations were measured using reversed-phase high-performance liquid chromatography, as described previously by Stenhoff et al. [12].

Patients were assessed for adverse events throughout the study by patient interviews and history or physical examinations. The primary safety endpoints were the proportion of patients with either a doubling of serum creatinine concentrations from baseline or an increase

Table 1. Clinical and biochemical data at baseline and after increasing the dosage of candesartan cilexetil from 16 to 160 mg/day in 12 patients with proteinuria[a]

	Time point/candesartan, mg/day					
	baseline 0	week 1 16	week 2 16	week 4 64	week 6 160	week 8 160
Serum Cr, mg/dl	2.0 ± 0.5	1.9 ± 0.6	1.9 ± 0.5	2.0 ± 0.6	2.0 ± 0.7	2.0 ± 0.5
Serum K^+, mEq/l	4.8 ± 0.5	4.7 ± 0.4	4.8 ± 0.4	4.9 ± 0.7	5.1 ± 0.7	4.9 ± 0.7
Urine Na^+, mEq/l	151 ± 79			160 ± 91		159 ± 59
Urine K^+, mEq/l	65 ± 26			56 ± 30		66 ± 21
Creatinine clearance, ml/min	55 ± 16	–	–	44 ± 19	–	49 ± 23
Urine protein, g/day	4.24 ± 3.8			3.35 ± 3.2		2.98 ± 3.3
Systolic BP, mm Hg	138 ± 17	136 ± 12	135 ± 16	138 ± 17	130 ± 17	127 ± 17[b]
Diastolic BP, mm Hg	84 ± 13	83 ± 14	82 ± 11	83 ± 8	81 ± 10	77 ± 13[b]
Mean arterial pressure, mm Hg	102 ± 13	101 ± 11	100 ± 9	101 ± 9	97 ± 10	94 ± 12[b]

Cr = Creatinine; K^+ = potassium; Na^+ = sodium; BP = blood pressure.

[a] Values are mean ± SD.

[b] $p < 0.05$ week 8 vs. baseline.

in serum K^+ levels to ≥6.0 mEq/dl. Patients with serum creatinine concentrations greater than twice the baseline value for two consecutive weeks were discontinued from the study. Nutritional counseling was provided for patients with serum K^+ levels ≥5.5 mEq/dl. Subjects with elevated serum K^+ levels were re-measured within 5 days. Any subjects whose serum K^+ levels remained >6.0 mEq/l were discontinued from the study.

Statistical Analysis

Values are reported as mean ± 1 SD. Differences from baseline (time 0) to the end of the study period (week 8) were analyzed using Student's two-sided t-test. Significance was set at a p value of <0.05.

Results

Twelve patients with chronic kidney disease were included in this pilot study. The patients ranged in age from 36 to 82 (mean 57 ± 14) years, 10 were male, 9 had a history of hypertension, 4 had diabetes, and 8 had non-diabetic-related renal disease of various etiologies or nephrosclerosis. Most patients were on additional antihypertensive medications including diuretics, calcium channel blockers, β-blockers and clonidine.

All patients completed the entire 8-week study period. At baseline, mean serum creatinine and K^+ levels were 2.0 ± 0.5 mg/dl and 4.8 ± 0.5 mEq/l, respectively (table 1). No significant change was seen in either of these parameters during the study (fig. 1). No patient met the predefined endpoint of a doubling of serum creatinine levels from baseline. Three patients had serum K^+ levels of >5.5 mEq/l at 64 and 160 mg/day at weeks 4 and 8. Two patients had serum K^+ levels of 6.1 mEq/l at week 6 (increases of 0.3 mEq/l from week 4); however, following nutritional education, these levels decreased within 5 days. Urinary sodium and K^+ excretion did not change ($p > 0.05$) from baseline to week 8 (table 1).

The mean systolic BP (SBP) at baseline was 138 ± 17 mm Hg, and the mean baseline diastolic BP (DBP) was 84 ± 13 mm Hg. By the end of the study, the mean SBP had decreased by 10 ± 14 mm Hg ($p < 0.05$) and the mean DBP had decreased by 7 ± 10 mm Hg ($p < 0.05$) from baseline (table 1).

The average 24-hour urinary protein excretion was 4.24 ± 3.8 g/day at baseline. This value decreased by 31 ± 35% at week 8 ($p < 0.05$) after 4 weeks of candesartan at 160 mg/day (table 1).

Plasma trough candesartan concentrations averaged 674 ± 557 nmol/l at 64 mg/day (n = 10) and 1,270 ± 639 nmol/l at 160 mg/day (n = 10) (fig. 2). Molar ratios of CV-15959 over candesartan concentrations in urine samples were variable between patients, but showed a high consistency within each patient at 64 and 160 mg/day (fig. 3).

No patients enrolled in the study demonstrated serious adverse events that required withdrawal from the study or dose reductions. Adverse events unrelated to serum K^+ and creatinine levels were observed in 6 patients during the protocol, although none of which were believed to be serious or drug-related (table 2). All adverse events were followed for 4 weeks after the last visit.

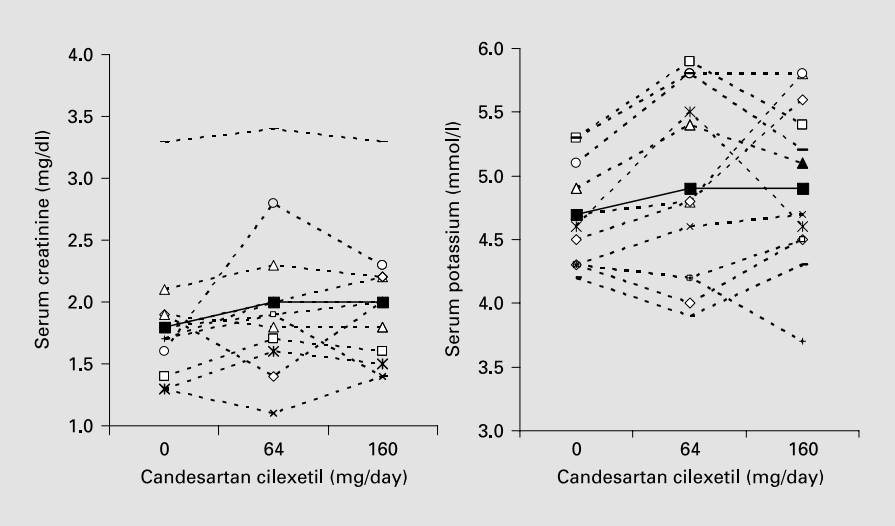

Fig. 1. Individual serum creatinine and potassium concentrations are reported at baseline, 64 (week 4) and 160 mg/day (week 8) of candesartan cilexetil in 12 subjects. The mean values are shown as dark bold squares.

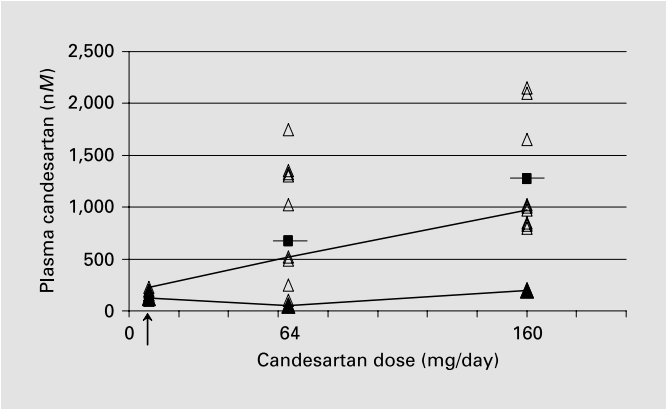

Fig. 2. Steady-state plasma trough concentrations (n*M*) of candesartan cilexetil at 64 and 160 mg/day are reported for 10 subjects. The mean values for the two doses are shown as dark bold squares. ↑ = Comparable plasma candesartan concentrations at 8–12 mg/day, from a previous study, are reported [18].

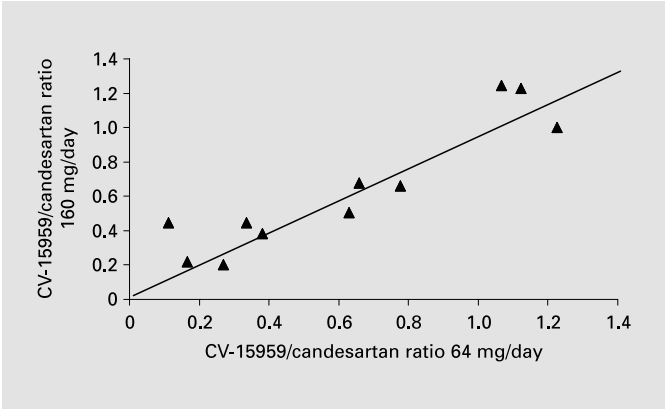

Fig. 3. Metabolite of candesartan (CV-15959) to drug (candesartan cilexetil) concentration ratio in urine during 64 and 160 mg/day of candesartan cilexetil in 11 subjects. Solid line represents the line of identity.

Table 2. Reported adverse events during the 8-week study period

Side effect	Incidence	Outcome
Vasovagal episode	1	Acute, resolved with change in posture
Leg cramps	1	Present before study, occurred intermittently during study
Atrial arrhythmia	1	Transient, resolved after 1 day
Peripheral edema	1	Resolved by 4 days
Epistaxis	1	Resolved by 2 days
Cellulitis and hand tremors	1	Cellulitis was treated with antibiotics, and hand tremors resolved

Discussion

The results of this study indicate that dosages of candesartan, well above the currently approved range of 8–32 mg/day, are safe and well tolerated among patients with diabetic and non-diabetic chronic kidney diseases. This is the first study to demonstrate that use of supramaximal doses of an ARB is safe and well tolerated, and thus offers a potential strategy to titrate the dose of an ARB, beyond maximally approved dosages, in order to achieve further reductions in proteinuria. This concept is important because the level of proteinuria is an independent risk factor for the progression of renal disease [13].

In this study, administration of high doses of the trial medication was characterized by minimal adverse events, with all patients completing the 8-week study period at 160 mg/day dosage of candesartan. This study supports the results of other trials, which have found no dose-related increases in adverse events with ARB therapy [14–16]. The tolerability advantages of ARBs over ACE inhibitors may make high-dose ARB therapy a more attractive option compared with high-dose ACE inhibitors, which can be associated with cough [17].

There was a trend for serum K^+ levels to be increased at the highest dose, as previously reported, but it was not significant [16]. In the 2 subjects with hyperkalemia, the K^+ levels dropped below 6 mEq/l within 5 days. Because aldosterone was not measured in this study, it is not known if high doses of candesartan would further reduce aldosterone secretion, thus having an additional effect on K^+ secretion. Because the potential for blockade of K^+ secretion has been considered a possible adverse effect of high doses of ARBs, patients at risk for hyperkalemia should be monitored appropriately.

This study evaluated candesartan plasma levels after 64 and 160 mg/day, considerably higher than traditional dosages of 8–32 mg/day. Plasma drug levels suggest that candesartan follows linear pharmacokinetics at these high doses, such that the extent of drug exposure in the individual is proportional to the dose given (fig. 2). For comparison, maximal plasma candesartan concentrations, following repeated administrations (8–12 mg/day), are in the range of 100–250 nmol/l, which is consistent with our results based on trough values [18]. The variability of plasma candesartan concentrations between subjects may be explained to some extent by differences in plasma protein binding. Because candesartan has a high binding degree to plasma proteins of about 99.7% [19], saturation of plasma binding following increases in doses would be expected to lead to exponential or non-linear increases in plasma concentrations. Since this was not observed, it can be concluded that saturation of plasma binding did not occur in this protocol.

In this pilot protocol, the ratio of metabolite-to-drug urine concentrations was variable between subjects, as has been previously reported in healthy patients [20]. Nonetheless, metabolite-to-drug urine ratios were very consistent within subjects across the two doses of candesartan and was indicative of linear, dose-independent pharmacokinetics (fig. 3).

Despite the proven effectiveness of standard doses of ACE inhibitors in the prevention and treatment of renal complications, kidney disease continues to progress, albeit at a slower rate [21]. One reason for this progression may be that currently approved doses of ACE inhibitors or ARBs do not completely block the RAS [7]. In theory, a greater renoprotective effect may occur by using higher doses of ARBs for a more complete blockade of the intrarenal RAS [11]. This pilot study was not designed to establish the dose-response relationship of candesartan for either the maximal reduction of proteinuria or BP because the short time intervals (2–4 weeks) were not sufficient. Further, the findings in this study are limited because of the small number of subjects (n = 12) and was only tested in subjects with moderate kidney disease (creatinine clearance rate of 30–70 ml/min; serum creatinine <3 mg/dl). However, the findings in this study provide important safety data allowing for supramaximal doses of ARBs to be tested in a larger patient population to examine the effects of a more specific and complete blockade of the RAS on urinary protein excretion and renal disease progression. Two multicenter trials (SMART, candesartan up to 128 mg; DROP, valsartan up to 640 mg) are currently underway to test this approach in patients with proteinuric renal disease.

The approved doses of ACE inhibitors and ARBs have previously been selected for their BP-lowering properties, not their antiproteinuric effects [6]. It is known that ARBs protect against the progression of renal disease in part through mechanisms independent of BP lowering [22, 23]. Forclaz et al. [24] demonstrated that supramaximal doses of the ARBs losartan and telmisartan, beyond those recommended for the treatment of hypertension, produce an increased inhibition of the RAS. In addition, Laverman et al. [15] have shown that ARBs and ACE inhibitors produce a dose-dependent decrease in proteinuria in patients with non-diabetic renal disease and that the combination of an ARB and ACE inhibitor produced a further reduction in proteinuria. More notably, the Irbesartan Microalbuminuria Trial (IRMA-2) [14] showed that the

highest dosage of irbesartan (300 mg/day) was more effective than a lower dosage (150 mg/day) in preventing the development of clinical proteinuria in patients with type 2 diabetes who have hypertension and microalbuminuria, despite similar BP lowering in both groups. It is now warranted to individually titrate the dose of ARBs in prospectively designed clinical trials to determine optimal methods for reducing proteinuria [2].

Conclusions

Overall, administering supramaximal doses of ARBs appears to be a promising strategy for determining the optimal antiproteinuric dose for patients with renal disease. Of note is the safety and tolerability of candesartan dosages up to 160 mg/day. Drug plasma levels indicate that exposure to candesartan increases in direct proportion to the dose given the patient, with no indication of saturable pharmacokinetics. The results from this pilot study support future trials to determine the clinical relevance of high-dose ARB therapy for slowing the progression of renal disease.

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