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The effect of high-dose angiotensin II receptor blockade beyond maximal recommended doses in reducing urinary protein excretion

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Abstract

The optimal doses of angiotensin-converting enzyme inhibitors (ACE-I) and/or angiotensin II receptor blockers (ARBs) for maximal reduction in urinary protein excretion are not known. Moreover, beneficial effects from ARBs, such as tissue protection owing to a more complete blockade of the renin-angiotensin-aldosterone system (RAAS), may be independent of blood pressure-lowering by ARBs. In this investigation, we evaluated whether increasing the dose of candesartan cilexetil, in subjects already on the maximally-recommended FDA doses of 32 mg, would induce a further reduction in 24-hour urinary protein excretion in patients with heavy proteinuria (urinary protein excretion >1.5 g/day; mean 4.4±2 g/day). Ten patients were started on 16 or 32 mg of candesartan cilexetil daily. After 1–2 months of therapy, the dose was titrated upwards to 96 mg. In all subjects, there were further reductions in 24-hour urinary protein excretion when the dose was increased beyond the recommended 32 mg maximal dose. Increasing the dose of candesartan cilexetil to 96 mg was safe, as most subjects showed no changes in serum potassium and, as expected, only a slight increase (0.5–0.7 mg/dl) in serum creatinine. These data warrant further investigation, since some subjects may require higher doses of candesartan to achieve optimal regression of proteinuria.

Introduction

Despite aggressive blood pressure (BP) control, progression to end-stage renal disease still occurs in patients with diabetic or non-diabetic renal disease. Blockade of the tissue and circulating renin-angiotensin system (RAS) has been identified as one of the most important strategies to limit the progression of chronic renal disease. Furthermore, blockade of the RAS has been shown to have renoprotective effects that are independent of BP control.[1] However, the optimal doses of angiotensin-converting enzyme inhibitors (ACE-I) and/or angiotensin II receptor blockers (ARBs), as well as the optimal therapeutic dosing intervals needed to induce maximal reduction in proteinuria, are not known. Previously, investigators have chosen doses of ACE-I and/or ARBs to block the tissue RAS by measurement of maximal beneficial effects on BP control.[2]

In order to effectively block the circulating and tissue RAS, clinical studies have demonstrated that using doses greater than those required for BP reduction may be beneficial to arrest the progression of renal disease.[3-6] Strategies to enhance blockade of the tissue RAS may result in greater renoprotective effects, by further reducing intraglomerular hydrostatic pressure and glomerular hypertrophy, and providing additional improvements in glomerular permselectivity. Our preliminary (unpublished) observations demonstrated that using supramaximal doses of ARBs (losartan, valsartan, irbesartan and candesartan) resulted in additional reductions in microalbuminuria in subjects with both diabetic and non-diabetic renal disease. Utilising ARBs rather than ACE-I was chosen owing to evidence that ARBs provide enhanced tissue RAS blockade by prevention of the 'ACE escape' phenomenon and thus more complete blockade of angiotensin II (Ang II) produced by both ACE and non-ACE pathways.[7-8] Furthermore, the excellent tolerability profile of ARBs compared with ACE-I was considered important when using supramaximal doses of these drugs.Therefore, we investigated whether increasing the dose of candesartan cilexetil in subjects already on maximally recommended FDA doses (32 mg) would further enhance the antiproteinuric effect and thereby preserve renal function in subjects with heavy proteinuria.

Methods

Ten older patients (67±10 years; 80% male) with heavy proteinuria (>1.5 g/day) were started on 16 or 32 mg of candesartan cilexetil daily. Several patients had renal biopsies performed. In this clinical observation, eight patients had nephrotic syndrome, four of whom had diabetic nephropathy, two had focal sclerosis, one had membranous nephropathy, and one had post-infectious nephropathy. The two other patients had nephrosclerosis, one being extremely severe and associated with moderate interstitial disease. Most of the patients were already receiving multiple medications for optimal BP control which included the following: calcium channel blockers (CCBs, 80%), diuretics (70%), beta-blockers (40%), alpha-blockers (40%), and ACE-I (40%). Additional concurrent medications included lipid-lowering agents, anti-ischaemic drugs and hypoglycaemic agents. No effort was made to standardise any class of medications other than ARBs, and no other controls, such as

sodium restriction, were instituted as patients were treated using standard office practice procedures. After 1–2 months of therapy, the dose of candesartan cilexetil was titrated upwards (at 16–32 mg dose increments) to 96 mg, while 24-hour urine samples were obtained to measure protein and creatinine. The candesartan doses were increased independently of the need for BP control. Subsequently, the effect of increased doses of candesartan on 24-hour urinary protein and creatinine excretion, BP, serum creatinine and potassium were serially measured.

It is important to note that this was not a prospective study, but a series of clinical observations in patients with heavy proteinuria. Some data is incomplete from the ten patients. Baseline data was utilised either prospectively or from past patient records collected close to the time of the clinical observation period. Furthermore, patients were observed in a normal clinical practice setting and complete data collection (e.g., blood testing) was not necessarily obtained at each office visit. Thus, no statistical analysis was performed but general trends are noted.

Results

Patients in this clinical report were characterised as normotensive (139±25/80±10 mmHg systolic/diastolic BP) with reduced renal function (estimated creatinine clearance rate of 69±24 ml/min). The effect of increased doses of candesartan cilexetil demonstrated progressive reductions in 24-hour urinary protein excretion (g/day) beyond the 32 mg maximal dose for candesartan cilexetil (Figure 1).

The 24-hour urinary protein excretion data are presented in Table 1 for individual patients and summarised as the mean±SD.

Systolic and diastolic BP appeared similar across all doses of candesartan, although some individuals demonstrated further reductions in BP at doses greater than 32 mg. Additionally, serum creatinine tended to increase by 0.5–0.7 mg/dl at the higher doses of candesartan, although the increase was attributable primarily to two of the ten patients. On the other hand, serum potassium was remarkably consistent, showing similar values from 4.3–4.5 mmol/l throughout the dosing range of candesartan.

Discussion

Strategies employed to enhance RAS blockade may be important to preserve existing renal function in patients with progressive renal disease. Utilising high-dose ARB therapy, above the doses already known to result in no further reductions in BP, may help to further reduce proteinuria and preserve residual renal function. We observed that, when the dose of candesartan cilexetil was extended beyond the recommended 32 mg maximal dose, there were further reductions in urinary protein excretion in all subjects. The

Figure 1 The effect of high-dose candesartan cilexetil (up to 96 mg) in reducing 24-hour urinary protein excretion (g/day). N=4–10 subjects per data point (see Table 1 for individual patient data). Data is presented as mean±SEM.

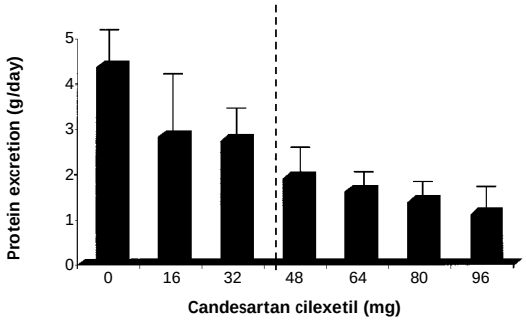

Table 1 Individual 24-hour urinary protein excretion rates (g/day).

		Protein excretion (g/day)						
Candesartan cilexetil dose (mg)		**0**	**16**	**32**	**48**	**64**	**80**	**96**
Patient	1	7.7	-	6.4	-	3.0	1.4	-
	2	6.5	6.4	4.6	5.8	4.7	2.4	-
	3	2.9	-	1.2	1.2	0.7	0.6	0.7
	4	3.7	-	1.1	0.9	1.7	0.9	0.6
	5	7.5	3.2	2.0	-	1.1	-	-
	6	1.7	1.1[+]	0.4[§]	0.2	0.4	0.5	0.2
	7	1.7	0.5[**]	0.8	0.2	0.2	0.3	-
	8	4.6	-	4.9	2.6	-	-	-
	9	-	-	3.3	1.7	1.3	1.6	1.8
	10	3.0	-	2.7	2.9	-	3.4	2.3
Mean		4.4	2.8	2.7	1.9	1.6	1.4	1.1
SD		2.4	2.7	2.0	1.8	1.5	1.0	0.9
N		9	4	10	8	8	8	5

Values are individual data and averaged (mean) data ± standard deviation (SD). N = number of patients; [+] Administered losartan (50 mg); [§] Administered irbesartan (300 mg); ** Administered irbesartan (150 mg).

additive antiproteinuric effect of high-dose candesartan was largely independent of reductions in BP.

In some patients, there were slight increases in serum creatinine when the dose of candesartan cilexetil was increased from 32 to 96 mg. However, candesartan was well-tolerated and appeared safe, since there were no increases in serum potassium values. Thus, using doses of candesartan cilexetil between 32 and 96 mg was safe and well-tolerated by the ten subjects, though the effect of high-dose ARB therapy and long-term safety must be more thoroughly evaluated in human subjects before any specific recommendations can be made regarding therapy.

It is difficult to speculate on the specific beneficial effect of higher doses of candesartan on urinary protein excretion, which may be influenced by many factors such as the aetiology of proteinuria, the magnitude of urinary protein excretion at baseline, use of multiple medications (e.g., ACE-I, CCBs, diuretics, beta-blockers, non-steroidal anti-inflammatory drugs [NSAIDs]), changes in systemic and glomerular pressures, salt intake, drug-protein binding, time-dependent effects and the length of dosing intervals.[1,9] This was a series of clinical observations and so we did not prospectively control for any of these factors. Nonetheless, the use of high-dose candesartan for the reduction of proteinuria may have specific advantages over ACE-I therapy because of a more complete blockade of the renal RAS due to the following three factors: 1) heightened intrarenal RAS activity, 2) the phenomenon of ACE escape and 3) activation of non-ACE pathways for the generation of angiotensin II.[7,10] Thus, there is sufficient scientific evidence to support greater RAS blockade with ARBs, thereby supporting enhanced benefit of high-dose candesartan therapy over ACE-inhibition.

In some patients, urinary protein excretion decreased in a dose-dependent fashion above 32 mg of candesartan cilexetil. On the other hand, one individual demonstrated no antiproteinuric response to candesartan cilexetil until 96 mg was administered. Thus, we conclude that some subjects may require higher doses of candesartan to achieve regression of proteinuria and optimally preserve renal function. In addition, we recognise that increasing the dose of ARBs may require several months for optimal reduction of urinary protein excretion. However, it is clear that these data warrant further investigation.

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