Kobe J. Med. Sci., Vol. 51, No. 1, pp. 1-6, 2005

Life-threatening Hyperkalemia during a Combined Therapy with the Angiotensin Receptor Blocker Candesartan and Spironolactone

HIDEKI FUJII [*†], HAJIME NAKAHAMA [*], FUMIKI YOSHIHARA [*], SATOKO NAKAMURA [*], TAKASHI INENAGA [*], and YUHEI KAWANO [*]

[*] *Division of Hypertension and Nephrology, National Cardiovascular Center, Suita, Osaka, Japan*

[†] *Division of Diabetes, Digestive, and Kidney Diseases, Department of Clinical Molecular Medicine, Kobe University Graduate School of Medicine, Kobe, Hyogo, Japan*

Received 11 April 2005/ Accepted 14 June 2005

Key words: Angiotensin receptor blocker, Candesartan, Spironolactone, Hyperkalemia

We describe a hypertensive nephrosclerosis patient presenting with severe hyperkalemia due to a combination therapy of the angiotensin receptor blocker (ARB) candesartan and spironolactone despite mildly decreased renal function. Recently, ARBs are replacing the ACE inhibitors. The combined therapy with ARB and spironolactone will eventually become the standard regimen. The strict attention and close monitoring of serum potassium should be mandatory in combination therapy to prevent hyperkalemia. Assessment of trans-tubular potassium gradient (TTKG) and fractional excretion of potassium (FEK) before starting the therapy would help in identifying the patients at higher risk of developing hyperkalemia. Co-administration of thiazide or loop diuretics is recommended to reduce the risk of hyperkalemia.

Evidences have been accumulating that promote the combination therapy of angiotensin converting enzyme (ACE) inhibitor with spironolactone as the standard regimen for the treatment of patients with heart failure and perhaps for those with essential hypertension [1]. Several reports showed spironolactone is effective for reducing proteinuria [2,3] and preventing tublointerstitional fibrosis [4]. As angiotensin receptor blockers (ARB) replace ACE inhibitors, the combined therapy of ARBs and spironolactone will eventually become the standard regimen for renal disease. However, there have been several reports that caution that simultaneous administration of ACE inhibitors and spironolactone may cause a higher risk of development of hyperkalemia [5]. As yet no cases of life-threatening hyperkalemia with the combined therapy of ARB and spironolactone despite mildly decreased renal function have been reported. We describe a nephrosclerosis patient presenting with severe generalized muscle weakness and electrocardiographic evidence of severe hyperkalemia in association with a combination therapy of the ARB candesartan and spironolactone despite mildly decreased renal function.

CLINICAL CASE

A 57-year-old woman was admitted from November 26, 2001 through December 20, 2001 because of hypertension and proteinuria. The hypertension had been noted 10 years before. On admission, her blood pressure was 210/102mmHg. Her pulse rate was 60

Phone: +81-78-6382-5111 Fax: +81-78-6382-6509 e-mail: hideki-f@tg7.so-net.ne.jp

beats/min and regular. Her electrocardiogram (ECG) was normal. Her renal function was mildly decreased with serum creatinine of 1.0mg/dl and 24-hour creatinine clearance of 72ml/min. Serum potassium was 4.2mEq/l, plasma renin activity (PRA) 2.6ng/ml/h (normal 0.5-2.5) and plasma aldosterone 20.5ng/dl (normal 3-16). A renal biopsy revealed tubular atrophy, mild mesangial cellular proliferation, interstitial fibrosis with leukocytes infiltration and an atherosclerotic arcuate artery. (Figure 1A,B) These symptoms were compatible with a diagnosis of benign nephrosclerosis. She was discharged with a regimen of amlodipine besilate 5mg once daily, an angiotensin receptor blocker (ARB) candesartan cilexetil 8mg once daily, spironolactone 25mg once daily, metoprolol tartate 40mg three times daily, and doxazosin mesilate 1mg once daily. Spironolactone was prescribed to prevent a progression of the interstitial fibrosis and a decrement of proteinuria. Two months after the prescription, serum potassium was 4.3mEq/l.

On April 24, 2002, she was admitted with severe generalized muscle weakness and general fatigue. She was disoriented in place and time, apyrexial and bradycardiac (heart rate : 26 beats/min) with cold extremities. An ECG showed absent P waves, wide QRS and tall peaked symmetrical T waves in leads II, III, aVF, V4-V6. (Figure 2A) Her blood pressure was 138/76mmHg. In blood chemistry, blood urea nitrogen was 30mg/dl, creatinine 1.8mg/dl, sodium 136mEq/l, potassium 9.4mEq/l, chloride 107mEq/l, blood glucose 110mg/dl, albumin 3.9g/dl and phosphorus 3.2mEq/l. A complete blood count revealed leukocytosis (10,200/mm^3), hematocrit 41.1% and C-reactive protein 0.27mg/dl. Plasma aminotransferase, lactic dehydrogenase, creatine kinase and troponin I levels were all within normal limits. A rapid arterial blood gas analysis showed plasma pH 7.38, pCO2 36.2mmHg, pO2 93.0mmHg, and bicarbonate 21.0mEq/l, with an anion gap of 8mEq/l. (Table 1)

A temporary pacemaker was immediately installed and a nine-hour hemodialysis therapy followed, which reduced serum potassium level to 3.9mEq/l. After the hemodialysis, the muscle weakness and ECG abnormalities vanished completely and serum potassium level was not elevated. (Figure 2B, 3) After all the medications were washed out for 2 weeks, pertinent tests to assess the patient's renal potassium handling were performed. An arterial blood gas analysis showed plasma pH 7.36, pCO2 36.5mmHg, pO2 88.7mmHg, bicarbonate 24.1mEq/l. PRA was 1.2ng/ml/Hr, and plasma aldosterone was 7.7pg/ml. Serum sodium was 140mEq/l, potassium 4.3mEq/l, chloride 108mEq/l, blood urea nitrogen 17mg/dl, creatinine 1.1mg/dl, creatinine clearance 57ml/min. Trans-tubular potassium gradient (TTKG):[(urine K) x (plasma osmolality)]/[(plasma K) x (urine osmolality)] was 4.2 (normal 6.68±0.55 [6] or >10 in hyperkalemia [7]) and fractional excretion of potassium (FEK):100 x [(urine K) x (plasma creatinine)]/[(plasma K) x (urine creatinine)] was 6.8% (normal 10-20% [8]). The patient didn't take any medications which could potentially induce hyperkalemia, e.g. non-steroidal antiinflamamatory drugs (NSAIDs).

Besides refractory hypertension, the patient had an uneventful recovery and was discharged after 50 days. She has been receiving amlodipine besilate 5mg once daily, candesartan cilexetil 8mg once daily, azosemide 30mg once daily and doxazocin melate 1mg once daily to date without a recurrence of hyperkalemia.

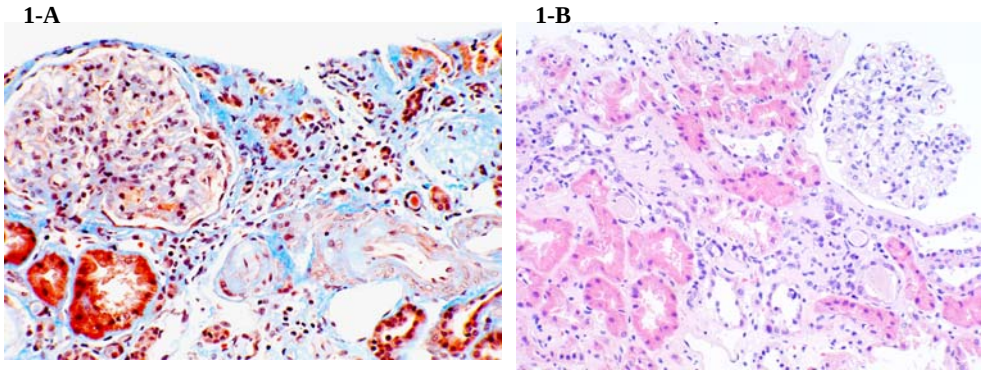

Figure 1A, B Light microscopy slides show mild mesangial cellular proliferation, interstitial fibrosis with leukocytes infiltration and an atherosclerotic arcuate artery.
A: Masson-trichrome stain. ×200 B: Hematoxylin and eosin (HE). ×200

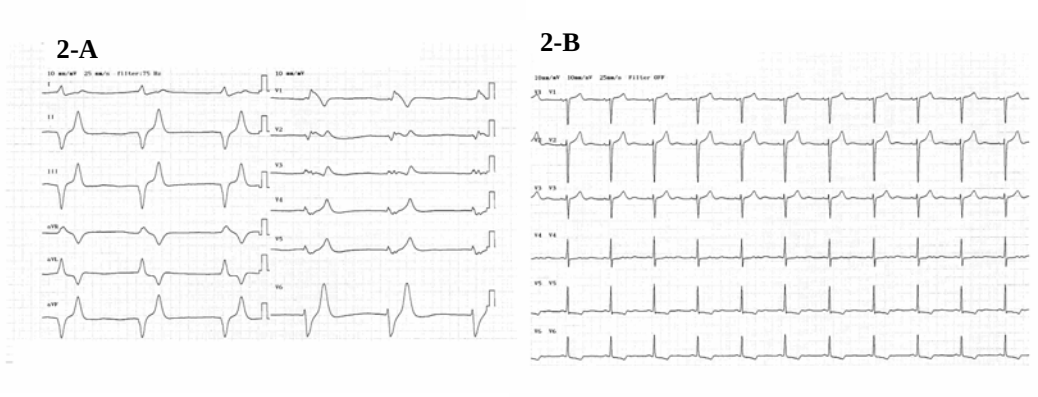

Figure 2A, B Electrocardiograms before and after hemodialysis.
a: Before hemodialysis b: After hemodialysis

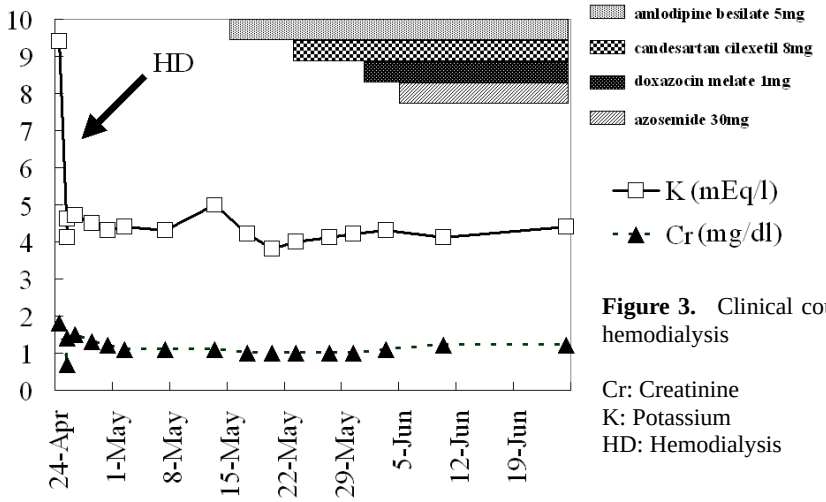

Figure 3. Clinical course after hemodialysis

Cr: Creatinine
K: Potassium
HD: Hemodialysis

Table 1. Laboratory data on admission

Hematology		**Arterial blood gas**	
White blood cells	10,200 /mm^3	pH	7.38
Red blood cells	418×10^4 /mm^3	pO_2	93.0 mmHg
Hemoglobin	13.6 g/dl	pCO_2	36.2 mmHg
Hematocrit	41.1 %	HCO_3^-	21.0 mEq/l
Platelets	21.4×10^4 /mm^3	Base excess	−3.1 mEq/l
Blood chemistry		Anion gap	8 mEq/l
AST	39 IU/l	**Urinalysis**	
ALT	34 IU/l	Protein	(+)
LDH	225 IU/l	Sugar	(−)
ALP	91 IU/l	Occult blood	(±)
γ-GTP	33 IU/l	RBC	1−3/HPF
Total bilirubin	0.9 mg/dl	WBC	0−1/HPF
Total cholesterol	142 mg/dl		
Triglyceride	116 mg/dl		
Total protein	6.8 g/dl		
Albumin	3.9 g/dl		
Blood urea nitrogen	30 mg/dl		
Creatinine	1.8 mg/dl		
Sodium	136 mEq/l		
Potassium	9.4 mEq/l		
Chloride	107 mEq/l		
Calcium	10.1 mg/dl		
Phosphate	3.2 mg/dl		
CRP	0.27 mg/dl		
Glucose	104 mg/dl		

AST：aspartate aminotransferase　ALT：alanine aminotransferase　LDH：lactate dehydrogenase
ALP：alkaline phosphatase　γ-GTP：γ-glutamyl transferase　CRP：C-reactive protein
HPF：high-power field

DISCUSSION

Patients presenting with hyperkalemia without oliguria or advanced renal failure are often diagnosed as having hyporeninemic hypoaldosteronism (renal tubular acidosis type IV). Our case had only mild renal dysfunction (24-h creatinine clearance 72ml/min). Because there was no metabolic acidosis on repeated arterial gas analyses, and plasma renin activity and plasma aldosterone levels were normal, we thought there was little possibility that she had renal tubular acidosis type IV. Trans-tubular potassium gradient (TTKG), the driving force for net potassium secretion, reflects mainly the bioactivity of aldosterone with regard to the kaliuretic response [7]. It has been reported that drug-induced hyperkalemia patients have lower TTKG values than those observed in patients with normal or mild-to-moderate renal failure [6]. In the present case, the TTKG and FEK were below normal, which indicated that her renal potassium handling was impaired. The impaired renal potassium handling might be attributed to the interstitial fibrosis revealed by a renal biopsy. A combined therapy of spironolactone and an ARB candesartan should have augmented the potassium retention and culminated in life threatening hyperkalemia (9.4mEq/l).

Hyperkalemia is a known complication of the use of ACE inhibitors. The incidence of hyperkalemia appears to be relatively low in patients with normal renal function (0-6%), but becomes increasingly common in those with renal insufficiency (5-50%). Development of life-threatening hyperkalemia during the use of ACE inhibitors, although relatively rare, has been reported. Additional factors reported to increase the risk of hyperkalemia during the use

of ACE inhibitors have included advanced age, congestive heart failure, and the use of potassium-sparing diuretic agents, potassium supplements, and NSAIDs. Long-acting ACE inhibitors are associated with an increased risk. On the other hand, the use of thiazide and loop diuretics were each associated with a reduced risk of hyperkalemia [9]. Indeed hyperkalemia has not recurred in our patient since she has been prescribed candesartan and a loop diuretic, azosemide.

It has been reported that, in the presence of renal insufficiency, an ARB valsartan did not raise serum potassium to the same degree as the ACE inhibitor lisinopril [10]. This difference in effect on serum potassium was related to a relatively smaller reduction in plasma aldosterone by valsartan and was not related to changes in glomerular filtration rate. Another study has shown no statistical differences in renal potassium handling between candesartan and lisinopril in patients with diabetes mellitus and preserved renal function [11]. Taken together, it can be deduced that ARBs that share many pharmacological properties with ACE inhibitors have a similar, if smaller, potential to induce hyperkalemia. Spironolactone, an aldosterone antagonist, also has a strong potential to induce hyperkalemia, especially in patients with renal impairment [12].

Clinical trials, especially 'The Randomized Aldactone Evaluation Study (RALES)' [1], have shown that addition of spironolactone to long-term ACE inhibitor therapy results in clinical improvement among patients with refractory heart failure. It is also reported that spironolactone in addition to ACE inhibitor resulted in a reduction of proteinuria in patients with chronic renal disease [2,4].

Though the risk of hyperkalemia remains a source of serious concern, this concern was not evident in the RALES trial, which reported an incidence of serious hyperkalemia of only 2% in the spironolactone treatment group that was not different from the 1% incidence observed in the placebo group. However, it's a fact that the publication of RALES was associated with abrupt increases in the rate of prescriptions for spironolactone and in the rate of hyperkalemia-associated morbidity and mortality [13]. In addition, this concern has been verified by a study of 25 patients with serious hyperkalemia caused by a combination of spironolactone and ACE inhibitors [5]. The defined serious hyperkalemia was a potassium concentration of >6.0mEq/l. The mean daily dose of spironolactone was 57mg and the mean serum creatinine concentration was 3.8mg/dl. The cause of renal insufficiency was dehydration and worsening of congestive heart failure. Two patients died, and 2 patients were resuscitated but survived. Hemodialysis was necessary in 17 patients and 12 patients were admitted to the intensive care unit. Our patient presented a similar clinical picture as the most serious cases in this report.

As ARBs are replacing ACE inhibitors, the combined therapy with ARBs and spironolactone will eventually become the standard regimen for renal disease. Caution and close monitoring of serum potassium is necessary in the combination therapy to prevent hyperkalemia. Assessment of TTKG and FEK before starting the therapy would be helpful in identifying patients at higher risk of developing hyperkalemia. Co-administration of thiazides or loop diuretics is recommended to reduce the risk of hyperkalemia.

REFERENCES

1. **Pitt B, Zannad F, Remme W et al.** 1999. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med **341**:709-717.
2. **Chrysostomou A, and Becker G.** 2001. Spironolactone in addition to ACE inhibition to reduce proteinuria in patients with chronic renal disease. N Engl J Med. **345(12)**: 925-926.

3. **Rachmani R, Slavachevsky I, Amit M, Levi Z, Kedar Y, Berla M, and Ravid M.** 2004. The effect of spironolactone, cilazapril and their combination on albuminuria in patients with hypertension and diabetic nephropathy is independent of blood pressure reduction: a randomized controlled study. Diabet Med **21(5)**:471-475
4. **Zhou X, Ono H, Ono Y, and Frohlich ED.** 2004. Aldosterone antagonism ameliorates proteinuria and nephrosclerosis independent of glomerular dynamics in L-NAME/SHR model. Am J Nephrol. **24(2)**:242-249
5. **Schepkens H, Vanholder R, Billiouw JM, and Lameire N.** 2001. Life-threatening hyperkalemia during combined therapy with angiotensin-converting enzyme inhibitors and spironolactone: an analysis of 25 cases. Am J Med.**110**:438-441.
6. **Mayan H, Kantor R, and Fartel Z.** 2001. Trans-tubular potassium gradient in patients with drug-induced hyperkalemia. Nephron **89**:56-61.
7. **Halperin ML, and Kamel KS.** 1998. Potassium. Lancet **352**:135-140.
8. **Take C, Ikeda K, Kurasawa T, and Kurokawa K.** 1991. Increased chloride reabsorption as an inherited renal tubular defect in familial type II pseudohypoaldosteronism. N Engl J Med **354**:472-476.
9. **Reardon LC, and Macpherson DS.** 1998. Hyperkalemia in outpatients using angiotensin-converting enzyme inhibitors. Arch Intern Med. **158**:26-32.
10. **Bakris GL, Siomos M, Richardson D, et al.** 2000. ACE inhibition or angiotensin receptor blockade: impact on potassium in renal failure. Kidney Int **58**:2084-2092.
11. **Preston RA, Baltodano NM, Alonso AB, and Epstein M.** 2002. Comparative effects on dynamic renal potassium excretion of ACE inhibition versus angiotensin receptor blockade in hypertensive patients with type II diabetes mellitus. J Clin Pharmacol **42**:754-761.
12. **Butler JV, McAvoy H, McEncroy D, and Mulkerrin EC.** 2002. Spironolactone therapy in older patients – the impact of renal dysfunction. Arch Gerontol Geriatr. **35**:45-49.
13. **Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, and Redelmeier DA.** 2004. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med. **351(6)**:543-551.