

Case Report

An Angiotensin Receptor Blocker and Spironolactone Enabled A Withdrawal from Furosemide and KCl in A Patient with Pseudo-Bartter's Syndrome

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A 30-year-old woman with pseudo-Bartter's syndrome was referred to our department because of hypokalemic symptoms caused by outrageous abuse of furosemide and by KCl infusion administered to compensate for it. As an attempt to break this vicious cycle, we first tried to change furosemide with azosemide, a long-lasting loop diuretics, to avoid acute excessive diuresis and excretion of potassium. Administration of losartan effectively attenuated the concentration of extremely activated plasma aldosterone. Administration of spironolactone reduced aldosterone breakthrough induced by losartan and the patient was released from both furosemide and KCl. Blocking renin-angiotensin-aldosterone system demonstrated to be an effective treatment for pseudo-Bartter's syndrome by the improvement of the total body potassium level which was decreased before treatment.

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Introduction

Pseudo-Bartter's syndrome caused by abuse of diuretic has manifestations similar to those in Bartter's syndrome. In both syndromes, depletion of intravascular volume stimulates the renin-angiotensin-aldosterone system (RAAS) and results in the development of hypokalemia.

Here we report a case of pseudo-Bartter's syndrome in which the use of angiotensin receptor blocker (ARB) and spironolactone enabled the withdrawal from an extremely large amount of furosemide and KCl with an increase in total body potassium.

Case report

A 30-year-old Japanese woman was referred to our hospital on February 19, 2003 for reducing a huge amount of furosemide and KCl. She had a family history of ulcerative colitis in her mother and drug allergy in her parents. She was diagnosed as having bronchial asthma at the age of 12 years. She frequently had to be absent from school because of poor health conditions such as psychogenic vom-

iting, hyperventilation or schoolphobia. She was also frequently admitted in and discharged from hospital because of proteinuria, microscopic hematuria, tonsillitis and bronchial asthma. In July 1995, she was diagnosed as non-IgA chronic glomerulonephritis by renal biopsy and she has been administered 10 mg/day of prednisolone. Since August 1998 the patient began to complain of oliguria and the doctor prescribed furosemide to her. She insisted on taking diuretics being obsessed by the idea that she would be dyspneic without furosemide. Actually, the patient refused doctor-in-charge's proposal and frequently requested the injection of furosemide; she became dyspneic with wheezing if the doctor hesitated the injection. However, if the response of furosemide was too strong and rapid, she complained of various hypokalemic symptoms such as weakness or numbness of extremities, abdominal pain and chest oppression, and she was never satisfied until nurse put more KCl into the ivh (intravenous high calorie infusion) bottle. As a result, the amount of furosemide and KCl increased reaching in 2001 the maximum dose of 160 mg/day iv of furosemide and 640 mEq/day ivh of KCl, respectively.

The patient visited our outpatient clinic in 2002 during she was in other hospital for evaluation of the state. We explained her as the

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second opinion that she had been fallen into malignant cycle resulted from the unnecessary use of diuretics. Administration of azosemide instead of furosemide made it possible to reduce gradually the amount of furosemide and KCl; we, however, could not decrease the dose of furosemide less than 48 mg/day iv or 40 mg/day per os or KCl less than 320 mEq/day ivh. Further investigation was required to rid the patient of the malignant cycle completely and she was referred to our department.

Physical examination on admission revealed that she was obese (163 cm in height and 71 kg in body weight), had normal blood pressure (126/78 mmHg) and regular pulse rate of 90 beats/min. Moon face and second degree swelling of palatine tonsils were noticed. Examination of the heart, lungs and abdomen was unremarkable except for striae cutis.

The blood test revealed: hemoglobin—14.0 g/dL; hematocrit—41.3%; platelet count— $28.5 \times 10^4/\mu\text{L}$; and white blood cell count— $6,700/\mu\text{L}$. The results of biochemical examination were as follows: total protein—7.4 g/dL; albumin—4.7 g/dL; sodium—144 mmol/L; potassium—4.0 mmol/L; chloride—107 mmol/L; magnesium—0.82 mmol/L; calcium—2.45 mmol/L; inorganic phosphorus—0.84 mmol/L; urea nitrogen—8 mg/dL or $286\mu\text{mol/L}$; creatinine—0.6 mg/dL or $53\mu\text{mol/L}$; aspartate aminotransferase (AST)—18 IU/L; alanine aminotransferase (ALT)—23 IU/L; lactate dehydrogenase (LDH)—136 IU/L; creatine kinase (CK)—52 IU/L. The urinary electrolytic concentration was as follows: sodium—74 mmol/L; potassium—73.8 mmol/L; and chloride—148 mmol/L. The plasma renin concentration (57.9 pg/mL [normal range: 9.8-31.3]) and plasma aldosterone concentration (PAC) (2,111 pg/mL [36-240] or 585.6 nmol/L [10.0-66.6]) were extremely elevated. In contrast, the total body potassium was very low (76.83 ± 3.36 gK [112-138] or 1.105 ± 0.049 gK/kg [1.56-1.98], values are expressed as mean \pm standard deviation) (Table 1). The total body potassium was determined by whole body count of K-40 (Fuji Electric Holdings Co., Ltd., Tokyo, Japan).¹

These data suggested that losartan, an ARB, would be effective since it has a property to block the elevation in RAAS. At first, intravenous furosemide was tapered from 48 mg/day and was replaced with increment of oral furosemide, then a very small dose of losartan (6.25 mg/day) was administered to avoid excessive drop in blood pressure. We could increase the dose of losartan stepwise up to 75 mg/day (Figure 1). Administration of losartan made it possible to

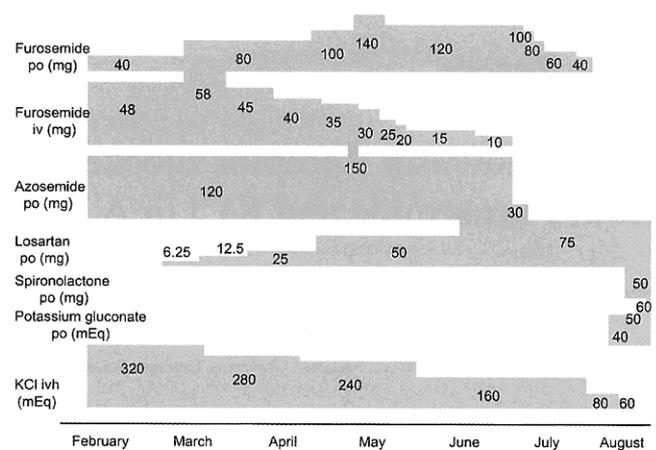


Figure 1. The time course of medication for the patient during the period she was hospitalized in 2003. Each figure presents the dose a day.

reduce both furosemide and KCl gradually. As we expected, PAC decreased to within normal range (150 pg/mL or 41.6 nmol/L) on April 7 and the total body potassium increased though remained subnormal (84.43 ± 3.54 gK or 1.268 ± 0.054 gK/kg) on May 27 (Table 1). We could discontinue the furosemide iv, azosemide per os and furosemide per os on June 30, July 2 and July 30 respectively; however, we could not lower the dose of KCl any more from 160 mEq/day. Re-elevation of PAC (552 pg/mL or 153.1 nmol/L) after 3-month treatment with losartan suggested that aldosterone breakthrough emerged. After the use of 50 mg/day of spironolactone, the patient became free from ivh on August 13 by stopping the administration of KCl, and PAC decreased to within normal range (57 pg/mL or 15.8 nmol/L) on August 18. Concentration of urinary electrolyte was almost normalized except potassium (sodium—24 mmol/L; potassium—46.7 mmol/L; and chloride—37 mmol/L) on August 8 (Figure 2). After the patient had been hospitalized for about half a year, she was discharged from our department with the prescription of 75 mg/day of losartan, 50 mg/day of spironolactone, and 60 mEq/day of potassium gluconate, while no ivh or loop diuretics.

Table 1. Changes in the total body potassium of the patient before, 3 months after and 1 year after the commencement of the treatment with losartan

Total body potassium ^a	On admission ^b February 19, 2003	During the time hospitalized ^c May 27, 2003	After discharge ^d February 25, 2004
Weight (gK)	76.83 \pm 3.36	84.43 \pm 3.54	84.42 \pm 3.56
Weight per body weight (gK/kg)	1.105 \pm 0.049	1.268 \pm 0.054	1.184 \pm 0.051

^aEstimated from the 20-minute measurement of whole body count of K-40. The values are expressed as mean \pm standard deviation. The reference value for total body potassium (per body weight) for Japanese woman in the thirties is 112-138 gK (1.56-1.98 gK/kg).

^bBefore the commencement of the treatment with losartan.

^cThree months after the commencement of the treatment with losartan.

^dOne year and 6 months after the commencement of the respective treatments with losartan and spironolactone.

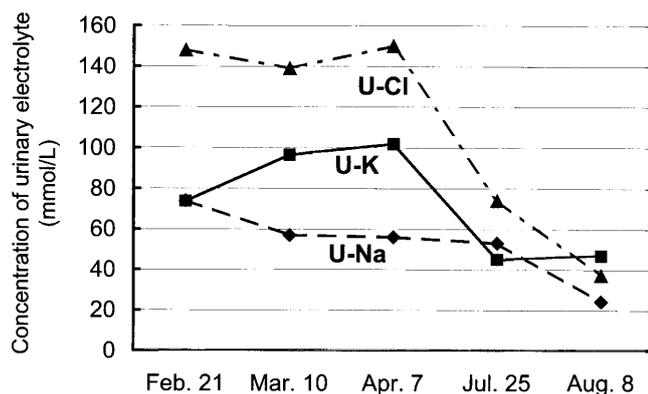


Figure 2. Changes in the concentration of urinary electrolytes: urinary sodium (U-Na), urinary chloride (U-Cl) and urinary potassium (U-K).

Discussion

Pseudo-Bartter's syndrome is most frequently observed in patients who habitually performed surreptitious vomiting or took diuretics.² The patient was not a paramedical personnel or a relative of physicians or nurses and was not a self-abusers as well. However, the doctors were not patient enough to persuade her not to increase the dose of furosemide, although she persistently asked for diuretics.

In order to break this vicious cycle, we first tried to change furosemide with azosemide, a long-lasting loop diuretics, to avoid acute excessive diuresis and excretion of potassium, and then administered losartan, which contributed to storage of potassium by suppressing extremely activated RAAS.

Hene et al.³ reviewed the effectiveness of ACE inhibitor in normalizing hypokalemia in Bartter's syndrome. However, no article has reported an improvement by ARB of the potassium metabolism in patient with pseudo-Bartter's syndrome. Since the major drawback of the use of ARB in patient with pseudo-Bartter's syndrome was considered to be severe hypotension that may accompany the initiation of treatment, we began with a very small dose of losartan (6.25 mg/day) and gradually increased the dose (Figure 1). PAC dramatically fell from 2,111 pg/mL (585.6 nmol/L) to 150 pg/mL (41.6 nmol/L) after 40-day treatment with losartan. Interestingly, the total body potassium had markedly been decreased in our patient before treatment, while 3-month treatment with losartan significantly though partially recovered from potassium loss caused by longstanding waste of renal potassium by furosemide (Table 1). Since more than 95% of potassium is in the intracellular space, we deemed measurement of total body potassium imperative for evaluating potassium metabolism. To our knowledge this is the first evidence that low-level serum potassium reflected a decrease in storage of body potassium and that ARB improved such a decrease, although only one report⁴ demonstrated effectiveness of enalapril against decreased total body potassium in patients with Bartter's syndrome.

Administration of spironolactone, potassium-sparing diuretics, also contributed to storage of potassium by attenuating PAC re-elevation after the treatment with ARB. The total body potassium 6 months after

discharge (February 25, 2004) was not different from one measured on May 27, 2003 (Table 1). Since we could withdraw KCl infusion completely (Figure 1), spironolactone must have worked effectively against the waste of renal potassium. The fall in PAC supported a beneficial effect of spironolactone. Recently, therapy with ACE inhibitor eventually re-elevated PAC (aldosterone breakthrough) in essential hypertension^{5,6} or in heart failure^{7,8} and PAC tended to increase as the treatment with ACE inhibitor lasted longer.^{9,10} Plasma aldosterone breakthrough was also found during long-term ARB therapy of heart failure,¹¹ whereas ARB did not induce aldosterone breakthrough in myocardium of hypertensive¹² or heart failure rats.¹³ We could not mention the aldosterone change in tissue level; however, our case suggested that not only ACE inhibitor but also ARB might cause plasma aldosterone breakthrough. Moreover, aldosterone blockade was mandatory for the treatment of the case in addition to attenuation of RAAS with ACE inhibitor or ARB.

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