Clin Exp Nephrol (2000) 4:67–70 © Japanese Society of Nephrology 2000

CASE REPORT

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Lobenzarit disodium-induced hyperkalemia successfully treated with fludrocortisone acetate

Received: November 4, 1998 / Accepted: June 10, 1999

Abstract A 65-year-old woman was admitted to our hospital because of hyperkalemia and renal dysfunction. Three months after she had been treated with lobenzarit disodium, a disease-modifying anti-rheumatic drug, her serum potassium and blood urea nitrogen levels rose. Neither calcium polystyrene sulfonate nor furosemide was effective in treating the hyperkalemia. On admission, she did not show metabolic acidosis and her creatinine clearance was 41 ml/min. Urinalysis results and urinary β_2-microglobulin and N-acetyl-β-D-glucosaminidase concentrations were normal. Her pituitary and adrenal functions and renin-aldosterone axis were also normal. A renal biopsy specimen demonstrated almost normal glomeruli and almost normal proximal tubules. On the other hand, the distal tubules demonstrated patchy atrophy with an increase in the interstitium and an infiltration of mononuclear cells. Fludrocortisone acetate, a synthetic mineralocorticoid, was effective in treating her hyperkalemia. The impaired responsiveness of the distal nephron to mineralocorticoid may have been the pathophysiological mechanism in this patient.

Key words Lobenzarit disodium · Hyperkalemia · Tubulointerstitial nephritis · Fludrocortisone acetate

Introduction

Lobenzarit disodium (CCA; N-(2)-carboxyphenyl-4-chloroanthranilic acid disodium) is a disease-modifying anti-rheumatic drug (DMARD) developed in Japan.[1,2] The most frequently occurring side effect of CCA is gastrointestinal upset, although nephrogenic diabetes insipidus, hyperkalemia, interstitial nephritis, and acute renal failure have also been reported.[3] Here, we report a unique case of hyperkalemia and tubulointerstitial nephritis induced by CCA; the patient was successfully treated with fludrocortisone acetate, a synthetic mineralocorticoid.

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Case report

A 65-year-old woman had been followed up in our hospital since visiting the Department of Orthopedics in March 1987 with complaints of finger stiffness, lumbago, knee-joint pain, and ankle-joint pain. She was diagnosed as having rheumatoid arthritis (RA) and osteoarthritis, and she was treated with fenbufen, at a dose of 600 mg/day. In December 1989, fenbufen was replaced by loxoprofen sodium, at a dose of 180 mg/day. In March 1991, she visited the Department of Internal Medicine because of hypertension. Nicardipine hydrochloride was prescribed, at a dose of 60 mg/day. The results of a laboratory examination conducted in October 1991 were: blood urea nitrogen (BUN), 19.8 mg/dl; serum creatinine (Scr), 0.7 mg/dl; serum sodium, 143 mEq/l; serum potassium, 4.7 mEq/l; and serum chloride, 101 mEq/l.

From January 27, 1993, she was treated in our department for both the arthralgia and the hypertension, and she received CCA at a dose of 240 mg/day, together with loxoprofen sodium. The results of a laboratory examination conducted on April 22, 1993 were: BUN, 38.7 mg/dl; Scr, 1.0 mg/dl; serum sodium, 139 mEq/l; serum potassium, 5.8 mEq/l; and serum chloride, 106 mEq/l. In October 1993, her serum potassium concentration had increased further, to 6.2 mEq/l, and calcium polystyrene sulfonate was administered, at a dose of 15 g/day. However, her serum potassium concentration remained high, often exceeding 5.0 mEq/l, and furosemide was prescribed, at a dose of 20 mg/day, in September 1994. The following month, her serum potassium concentration was still high (6.0 mEq/l),

and she was admitted to our hospital on November 17, 1994 for further evaluation and treatment of hyperkalemia.

Physical examination upon admission showed the following results: respiration rate, 14/min; body temperature, 36.5°C; pulse rate, 74/min; and blood pressure, 160/90 mmHg. The heart and lungs were normal on auscultation; the kidneys were not palpable, and there was no edema of the extremities. Laboratory findings on admission were: hemoglobin, 9.8 g/dl; hematocrit, 29.5%; white cell count, 4700/μl (neutrophils, 61.4%; lymphocytes, 27.2%; monocytes, 7.5%; eosinophils, 3.6%; basophils, 0.3%); platelets, 159000/μl; serum total protein, 7.4 g/dl; serum albumin, 4.2 g/dl; serum γ-globulin, 1.8 g/dl; BUN, 31.9 mg/dl; Scr, 1.4 mg/dl; serum sodium, 139 mEq/l; serum potassium, 5.1 mEq/l; serum chloride, 108 mEq/l; plasma osmolality, 295 mOsm/kg; erythrocyte sedimentation rate, 52 mm/h; C-reactive protein, 0.4 mg/dl; rheumatoid factor, 5 IU/ml; antinuclear antibody, negative; C_3, 79 mg/dl; C_4, 24 mg/dl; and CH_{50}, 42.7 U/ml. Dipstick analysis of urine was negative for protein, glucose, and occult blood, and urine pH was 6.5. The urinary sediment contained one red cell, three white cells, seven epithelial cells, and none or one hyaline casts per high-power field. Urine volume was 1820 ml/day; urinary excretion of sodium, potassium, and chloride was 158, 25, and 124 mEq/day, respectively; and the urinary anion gap (UAG) was 32.9 mEq/l. Fractional excretion of sodium (FE_{Na}) and potassium (FE_K) was 1.9% and 8.2%, respectively, and the transtubular potassium gradient (TTKG) was 2.6. Her serum β_2-microglobulin (β_2MG) concentration was 5.1 mg/dl, and urinary β_2MG and N-acetyl-β-D-glucosaminidase (NAG) concentrations were 64 μg/l and 5.2 U/l, respectively. Her creatinine clearance was 41 ml/min. Fishberg's urine concentration test showed a maximal urinary specific gravity of 1.012 (460 mOsm/kg). A phenolsulfonphthalein test (Chapman-Halsted method) gave a value of 11.4% at 15 min. Analysis of arterial blood gases at the ambient air showed: pH, 7.418; P_{CO_2}, 40.7 mmHg; P_{O_2}, 71.0 mmHg; bicarbonate, 26.5 mEq/l; and base excess, 2.5 mEq/l. Results of endocrine examinations were: plasma adrenocorticotropic hormone, 15 pg/ml (normal range [NR], 9–52 pg/ml); plasma cortisol, 10.1 μg/dl (NR, 4.0–18.3 μg/dl); plasma aldosterone concentration, 140 pg/ml (NR, 29.9–159 pg/ml); plasma renin activity, 2.5 ng/ml/per h (NR, 0.3–2.9 ng/ml/per h); and plasma antidiuretic hormone, 2.7 pg/ml (NR, 0.3–3.5 pg/ml). Urinary excretion of 17-hydroxycorticosteroid (NR, 2.4–11.0 mg/day) and 17-ketosteroid (NR, 2.2–7.3 mg/day) was 4.2 and 5.8 mg/day, respectively. Abdominal computed tomography (CT) scans and renal ultrasound revealed almost normal-sized kidneys with no hydronephrosis.

On the sixth day after admission, CCA, calcium polystyrene sulfonate, and furosemide were discontinued. On the 12th day, her BUN, Scr, and serum potassium levels had increased to 50.8 mg/dl, 1.4 mg/dl, and 6.0 mEq/l, respectively, and calcium polystyrene sulfonate was administered again. Based on the assumption that reduced responsiveness of the renal tubules to mineralocorticoid had caused volume depletion and hyperkalemia, we administered fludrocortisone acetate, a synthetic mineralocorticoid, at a dose of 0.05 mg/day, from the 15th day. On the 20th day, her serum potassium concentration had declined to 4.5 mEq/l and her face was slightly edematous; fludrocortisone acetate was therefore reduced to 0.04 mg/day (Fig. 1). On the 22nd day, her urinary excretion of sodium, potassium, and chloride was 94, 22, and 105 mEq/day, respectively, and UAG was 6.9 mEq/l. The FE_{Na} and FE_K were 0.8% and 5.4%, respectively, and the TTKG was 1.4. Analysis of arterial blood gases showed: pH, 7.379; P_{CO_2}, 47.3 mmHg; P_{O_2}, 75.0 mmHg; bicarbonate, 27.8 mEq/l; and base excess, 3.4 mEq/l. On the 28th day, an open renal biopsy was performed after we obtained her informed consent. Histopathological examination revealed almost normal glomeruli and proximal tubules. The distal tubules demonstrated patchy atrophy with an increase in the interstitium and infiltration of mononuclear cells (Fig. 2). Some distal tubules were dilated and contained hyaline casts, and they had a thyroid-like appearance. Arterioles and small arteries demonstrated mild fibroelastosis. There were no significant findings on immunofluorescence microscopy.

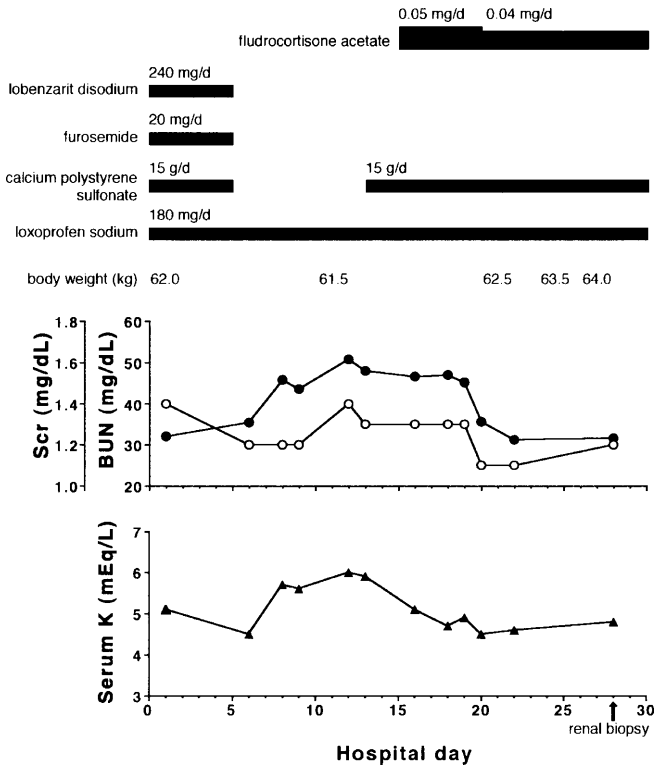

Fig. 1. Clinical course of the patient from admission to renal biopsy. Treatments are also listed. *BUN*, Blood urea nitrogen (*filled circles*); *Scr*, serum creatinine (*open circles*)

She was discharged on December 23, 1994, after 37 days of hospitalization. Calcium polystyrene sulfonate was reduced to 10 g/day from January 24, 1995 and to 5 g/day from March 7, 1995. Her serum potassium concentration remained below 5.0 mEq/l, and calcium polystyrene sulfonate was discontinued on June 20, 1995. Thereafter, she received only fludrocortisone acetate, at a dose of 0.04 mg/day, and her BUN, Scr, and serum potassium levels were 34.6 mg/dl, 1.0 mg/dl and 4.7 mEq/l, respectively, in August 1995. Her

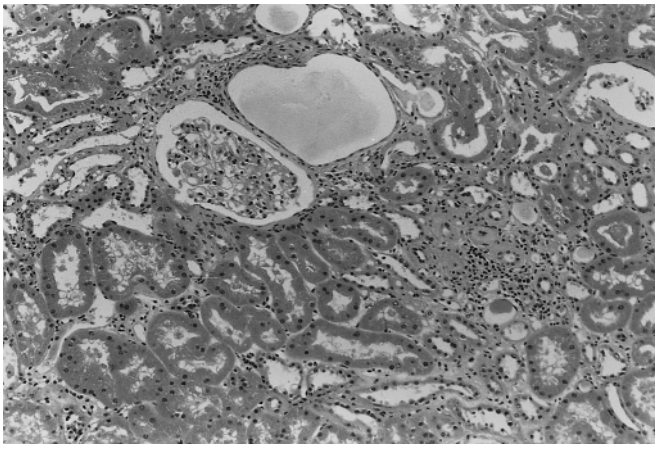

Fig. 2. Renal biopsy demonstrated almost normal glomeruli and proximal tubules, and patchy atrophy of distal tubules with an increase in the interstitium and infiltration of mononuclear cells. H&E, ×200

renal function and serum potassium level remained stable thereafter, but she was operated on for gall-bladder cancer in 1996 and died of its recurrence in 1997.

Discussion

CCA was developed in Japan and became accepted as a DMARD in Japan in 1986. However, several other long-acting drugs for treating RA have since become available, and the use of CCA has declined. There have therefore been very few reports in English on the side effects of CCA. Tubulointerstitial nephritis, nephrogenic diabetes insipidus, hyperkalemia, and acute renal failure have been reported in RA patients treated with CCA.[3] Two broad categories of renal disorders can be distinguished in RA: lesions caused by the disease itself and lesions occurring as a result of side effects of therapeutic agents. As an example of the former, secondary amyloidosis has been reported to occur in 5% to 10% of patients with long-standing arthritis.[4] The clinical course of amyloidosis in patients with RA is one of progressive renal failure. Nephrotic syndrome arises as a complication of either gold or penicillamine therapy. The renal histology associated with gold-induced proteinuria and nephrotic syndrome is membranous glomerulopathy.[5] Clinically and histologically, penicillamine-induced nephropathy is similar to gold nephropathy.[5] Nonsteroidal anti-inflammatory drugs (NSAIDs) are the mainstay of treatment for RA, and they can cause tubulointerstitial nephritis.[6] The average duration from the start of treatment to the onset of NSAID-induced tubulointerstitial nephritis is several months to 1 year. Nephrotic range proteinuria is found in more than 80% of patients with NSAID-induced interstitial disease. Although our patient had been treated with NSAIDs for 6 years before she received CCA, her urine was negative for protein. Therefore, it is plausible that CCA, rather than NSAIDs, caused tubulointerstitial nephritis in this patient.

As far as we know, this is the first case of CCA-induced hyperkalemia to be successfully treated with fludrocortisone acetate. An interesting point in the present patient is the relationship between her functional abnormalities and histological findings. Urinalysis results were normal, and urinary β_2MG and NAG concentrations, markers of the proximal tubule damage, were also normal. These findings are consistent with the histological findings of the glomeruli and proximal tubules. On the other hand, the distal tubules, where aldosterone acts, demonstrated patchy atrophy. A defect in urinary concentrating capacity suggests that there has been damage to the collecting duct. We have previously experienced a patient with primary aldosteronism (PA), due to an aldosterone-producing adenoma, associated with gouty kidney (unpublished observation). That patient became volume-depleted and hyperkalemic after an adrenalectomy and was successfully treated with supplementation of fludrocortisone acetate. We administered fludrocortisone acetate to the present patient based on the speculation that the pathophysiological mechanism was similar to that in the patient with PA mentioned above. Up to 90% of filtered potassium is reabsorbed by the time it reaches the beginning of the distal convoluted tubule. Urinary potassium excretion responds to intake primarily by regulating potassium secretion by the mid to late distal tubule and collecting duct. Aldosterone has a major regulatory effect on potassium excretion by the kidney. Patients with renal failure are able to maintain an almost normal serum potassium concentration despite a marked decrease in the glomerular filtration rate. The present patient had hyperkalemia out of proportion to the degree of renal failure. As her pituitary and adrenal functions and renin-aldosterone axis were normal, the primary defect may have been partial resistance to the physiologic effect of aldosterone to promote potassium secretion. Her low TTKG (<8) suggests that the collecting duct was not responding appropriately to the prevailing hyperkalemia and that potassium excretion was impaired.[7] Perez et al.[8] named such a syndrome "renal tubular hyperkalemia". This clinical entity has been found in patients with sickle cell disease, systemic lupus erythematosus, renal transplant, obstructive uropathy, acquired immunodeficiency syndrome, and a group of miscellaneous diseases, including chronic tubulointerstitial nephritis. Mineralocorticoid replacement represents the most logical approach to therapy in these patients.[9] Theoretically, a higher dose of furosemide together with a high salt intake to prevent volume depletion may have corrected the hyperkalemia, although this was not tried in the present patient. Although a sufficient dose of calcium polystyrene sulfonate may have been effective in treating the hyperkalemia, the patient found it difficult to tolerate. Sodium polystyrene sulfonate may have been more effective than calcium polystyrene sulfonate, because the former increases delivery of sodium to the distal potassium exchange site. Otherwise, free intake of potassium may have attenuated the effectiveness of calcium polystyrene sulfonate and furosemide, because her serum potassium concentration rose after the discontinuation of these agents on the sixth day after admission. On the other hand, of interest, in a patient with systemic lupus

erythematosus who presented with hyperkalemia, glomerulonephritis, and tubulointerstitial inflammation,[10] dietary potassium restriction and therapy with diuretics combined with cation exchange resins failed to reduce potassium levels sufficiently, but fludrocortisone treatment proved to be effective in correcting the potassium level. In the present patient, mineralocorticoid therapy reduced the potassium concentration without increasing urinary potassium excretion. This finding suggests that the mineralocorticoid stimulates potassium secretion across the distal colon[11] or increases the movement of potassium from extracellular to intracellular compartments.[9] Despite the ineffectiveness of fludrocortisone acetate in increasing urinary potassium excretion in our patient, urinary sodium excretion and FE_{Na} fell significantly.

Our patient did not show metabolic acidosis before the administration of fludrocortisone acetate. Some patients with renal tubular hyperkalemia present with hyperchloremic metabolic acidosis, while others do not.[7,8] About 50% of patients with hyporeninemic hypoaldosteronism exhibit metabolic acidosis. It is not known why not all patients with isolated hypoaldosteronism develop metabolic acidosis.[7] In the cortical collecting duct (CCD), mineralocorticoids stimulate Na^+ absorption, increasing the lumen-negative transepithelial potential and secondarily stimulating K^+ and H^+ secretion. In patients chronically treated with amiloride at doses expected to inhibit CCD acidification, metabolic acidosis does not develop. Therefore, it is possible that the medullary and papillary segments could compensate for an isolated voltage-dependent defect in CCD. On the other hand, hyperkalemia itself significantly reduces renal ammonium excretion and may play a role in the production of hyperchloremic acidosis.[7] The tendency for metabolic acidosis to develop as a consequence of hyperkalemia may depend on the extent of the remaining functional renal mass and the integrity of the renin-aldosterone system. Therefore, a defect in generating a favorable electrochemical gradient in the CCD would lead to hyperkalemia and varying degrees of hyperchloremic acidosis. The coexistence of hyperkalemia and hyperchloremic metabolic acidosis suggests generalized collecting duct dysfunction. Our patient's high UAG, which suggests the presence of altered distal urinary acidification or reduced ammonium excretion, was also decreased after mineralocorticoid therapy.

In summary, we have experienced a patient with CCA-induced hyperkalemia in whom tubulointerstitial nephritis affected mainly the distal nephrons, and for whom fludrocortisone acetate was effective in treating the hyperkalemia. The major points of interest in this case report are the renal side effects of CCA and strategies for their treatment.

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