CASE REPORT

Eplerenone Improved Hypokalemia in a Patient with Gitelman’s Syndrome

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Abstract

A 47-year-old woman presented with hypokalemia (2.4 mmol/L). She also had hypomagnesemia, hypocalciuria, and hyperreninemic hyperaldosteronism. Sequence analysis revealed a compound heterozygous mutation, R655C and R955Q, in the SLC12A3 gene. These findings were compatible with Gitelman’s syndrome (GS). Eplerenone, a selective aldosterone blocker, in combination with oral potassium chloride improved serum potassium level (3.6 mmol/L) with no apparent adverse effect. Although eplerenone has an advantage over spironolactone for its selective affinity for the aldosterone receptor, the efficacy and safety of eplerenone for GS is little understood. Our observation suggests that eplerenone is a useful treatment option for GS.

Key words: Gitelman’s syndrome, hypokalemia, SLC12A3 gene, eplerenone


Introduction

Gitelman’s syndrome (GS) is a rare autosomal recessive disorder characterized by hypokalemia, hypomagnesemia, metabolic alkalosis, and hypocalciuria (1-3). Most cases of GS are caused by homozygous or compound heterozygous loss-of-function mutations in the SLC12A3 gene encoding the thiazide-sensitive sodium chloride co-transporter (TSC), a pharmacological target of thiazide diuretics. The standard therapy for hypokalemia caused by GS is administration of potassium supplements and/or potassium-sparing diuretics such as spironolactone. However, spironolactone, a representative anti-aldosterone drug, often causes gynecomastia, erectile dysfunction, breast tenderness, hirsutism, irregular menstrual cycle, and irregular vaginal bleeding because it also binds to androgen and progesterone receptors (4, 5). On the other hand, eplerenone, a novel selective aldosterone blocker, is thought to solve this problem because eplerenone has lower affinity for these sex steroid receptors than spironolactone (5, 6). To date, the usefulness of eplerenone has been established in patients with cardiovascular disease and heart failure (7-9). However, the therapeutic efficacy and safety of eplerenone treatment to GS patients is little understood. Here, we report the case of a 47-year-old GS patient who was treated with eplerenone.

Case Report

A 47-year-old woman was referred to Nagoya Ekisaikai Hospital for further examination of hypokalemia (serum potassium level 2.4 mmol/L). Until then, she had been followed up by Nakayama Clinic because of diabetes and hyperlipidemia. She was given 0.9 mg of voglibose for diabetes. She was not an alcohol drinker and she did not take any other drugs, such as diuretics and laxatives, or supplements. She underwent a total hysterectomy because of uterine myoma at the age of 43 years. She was 153 cm tall and weighed 59 kg (body mass index 25.2 kg/m²). Her blood pressure was 102/68 mmHg. Muscle cramps and weakness were not observed. Blood examination results, including the baseline values of hormones during the morning hours, are summarized in Table 1. She also had hypomagnesemia and metabolic alkalosis. Urinalysis showed low levels of cal-

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Treatment with 100 mg eplerenone in combination with gradually increased to within the reference range under blood pressure values (Fig. 2). The serum potassium level was started. Doses of both drugs were carefully determined because long-term spironolactone treatment with eplerenone and oral potassium chloride is incidentally detected such as in the present case. Hypokalemia, it is reasonable that spironolactone or amiloride function of RAS is associated with the occurrence of hypokalemia. An increased plasma arginine vasopressin level also reflects volume contraction. Considering that the hyperfunction of RAS is associated with the occurrence of hypokalemia, it is reasonable that spironolactone or amiloride (not available in Japan) is mainly used for the treatment of hypokalemia.

Hypokalemia caused by GS is often asymptomatic and it may cause dangerous arrhythmias or sudden cardiac arrest (2, 12). However, correcting the serum potassium level was maintained above 1.5 mg/dL.

For the treatment of genetic diseases such as GS, long-term (probably life-long) medication is necessary. To minimize adverse effects, it is desirable that the effect of the therapeutic drug is limited only to the etiological factor(s). The selective anti-aldosterone drug, eplerenone, was administered to this patient because long-term spironolactone treatment might induce unexpected adverse effects.

Treatment with eplerenone and oral potassium chloride was started. Doses of both drugs were carefully determined on the basis of the monitored serum electrolyte level and blood pressure values (Fig. 2). The serum potassium level gradually increased to within the reference range under treatment with 100 mg eplerenone in combination with 2,400 mg oral potassium chloride, with no apparent adverse effect. Plasma renin activity and plasma aldosterone concentration increased to 35.4 ng/mL/h and 517 ng/mL, respectively. The serum sodium level was maintained above 135 mmol/L. Her blood pressure was maintained within safe levels. Magnesium oxide was also administered but it had to be discontinued because of diarrhea. However, serum magnesium level was maintained above 1.5 mg/dL.

### Discussion

Most patients with GS have loss-of-function mutations of TSC, which is mainly expressed in the distal convoluted tubule (DCT) in the kidney (1-3). At present, more than 100 distinct mutations have been identified. Sodium chloride re-absorption is impaired in DCT, and sodium remains in the collecting duct, resulting in volume contraction. This vascular volume reduction activates RAS and subsequently causes hypokalemia. An increased plasma arginine vasopressin level also reflects volume contraction. Considering that the hyperfunction of RAS is associated with the occurrence of hypokalemia, it is reasonable that spironolactone or amiloride (not available in Japan) is mainly used for the treatment of hypokalemia.
level is often difficult due to the excessive excretion of urinary potassium. The therapeutic approach for hypokalemia in this rare disease (prevalence, 1:40,000) has not been studied sufficiently. Colussi et al reported that spironolactone was more effective than amiloride in 6 GS patients (13). However, it is known that spironolactone also binds to several types of steroid hormone receptors and causes some adverse effects. Eplerenone is thought to overcome these drawbacks of spironolactone because it has a lower affinity for androgen and progesterone receptors (less than 1/100 of that for the aldosterone receptor). Because the present patient was a middle-aged woman whose menstrual periods had stopped since undergoing a total hysterectomy, treatment with spironolactone might not result in some of the major adverse effects of the drug, such as irregular menstrual cycle and irregular vaginal bleeding. However, life-long medication is necessary for the treatment of GS; therefore, drugs with fewer side effects should be

Figure 1. Sequence analyses. A and B, Results of direct sequencing of PCR fragments in exon 16 (A) and exon 25 (B) in the SLC12A3 gene of a control subject (left) and the study patient (right). A, A heterozygous point mutation of CGC to TGC in residue 1963 (arrow). This single-base substitution causes a replacement of arginine to cysteine at codon 655. B, A heterozygous point mutation of CGG to CAG in residue 2864 (arrow). This single-base substitution resulted in the replacement of arginine to glutamine at codon 955. C, Structure of TSC protein. TSC consists of 12 transmembrane domains and a long intracellular carboxy-terminal domain. The 2 mutated amino acids are located in the intracellular domain.

Figure 2. Clinical course. The serum potassium level was significantly increased after treatment with eplerenone in combination with oral potassium chloride.
used. Even if spironolactone presents no clinically overt side effect, the safety of long-term treatment with this drug is questionable because spironolactone completely binds to several types of steroid hormone receptors. Persistent binding for decades to these receptors may induce unexpected side effects. For example, in previous studies, spironolactone significantly increased plasma cortisol levels through binding to glucocorticoid receptor and increased HbA1c levels, compared with patients receiving eplerenone (14) or placebo (15). Because the present patient had diabetes and dyslipidemia, long-term spironolactone treatment may worsen her diabetes and other metabolic parameters. Therefore, she was treated with eplerenone rather than spironolactone. Indeed, eplerenone may have fewer advantages for this patient than for male or younger female GS patients; however, the clinical course of this case is useful for future treatment of GS patients.

Patients with GS are normotensive or relatively hypotensive (2). Because eplerenone is basically an antihypertensive drug, patients should be carefully followed to avoid the occurrence of hypotension. In the present case, 100 mg/day of eplerenone did not decrease blood pressure. Her blood pressure was maintained within safe levels throughout the clinical course.

Sufficient doses of aldosterone blocker and potassium chloride cannot increase the serum potassium level unless serum magnesium level is corrected. Although magnesium supplementation was discontinued because of intolerance, her serum magnesium level remained around the lower limit of the reference range (1.5-2.3 mg/dL). Conversely, in such cases, GS may be misdiagnosed. In a few GS patients, magnesium concentration is maintained in the reference range (16).

Few reports are available on the therapeutic efficacy and safety of eplerenone in patients with GS; Morton reported an improvement of hypokalemia in a female GS patient who was intolerant to spironolactone and amiloride (17). Thereafter, eplerenone was continued during her pregnancy (18). The effect of eplerenone treatment on many GS patients has not been evaluated yet. However, our observation suggests that eplerenone should be considered as a therapeutic option for GS. Moreover, eplerenone may also be effective for hypokalemia caused by other aldosterone disorders such as Bartter’s syndrome. According to the package insert, eplerenone is contraindicated when potassium supplements are administered simultaneously. The serum potassium level should be carefully monitored if both drugs are used.

The authors state that they have no Conflict of Interest (COI).

References