

[CASE REPORT]

Combination Therapy Using Sodium Zirconium Cyclosilicate and a Mineralocorticoid Receptor Antagonist in Patients with Heart Failure and Hyperkalemia

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Abstract:

Hyperkalemia is a challenging comorbidity to manage in patients with heart failure and chronic kidney disease, particularly when administering renin-angiotensin-aldosterone system inhibitors. We encountered an 88-year-old woman with hypertensive heart failure and chronic kidney disease. A mineralocorticoid receptor antagonist was able to be safely administered despite persistent hyperkalemia when sodium zirconium cyclosilicate, a non-absorbed, non-polymer zirconium silicate compound that preferentially exchanges hydrogen and sodium for potassium and ammonium ions in the gastrointestinal tract, was concomitantly administered. Sodium zirconium cyclosilicate might be a promising therapeutic tool to use in order to administer mineralocorticoid receptor antagonist safely in patients with heart failure, chronic kidney disease, and hyperkalemia.

Key words: heart failure, potassium, hemodynamics

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Introduction

Mineralocorticoid receptor antagonists (MRAs) including spironolactone and eplerenone are optimal medical therapies that improve the survival in patients with heart failure and a reduced ejection fraction (1, 2). Furthermore, spironolactone might be an effective therapy for patients with heart failure and a preserved ejection fraction (3). Recently, esaxerenone has been studied as a third-generation MRA, particularly for patients with hypertensive heart failure (4). However, clinicians sometimes hesitate to initiate MRAs in patients with hyperkalemia, such as those with chronic kidney disease, and concomitant use of renin-angiotensin system inhibitors (5, 6).

Recently, sodium zirconium cyclosilicate (SZC), a non-absorbed, non-polymer zirconium silicate compound that preferentially exchanges hydrogen and sodium for potassium and ammonium ions in the gastrointestinal tract, has become clinically available to treat hyperkalemia (7, 8). We hypothesized that SZC might be a promising therapeutic tool to

safely initiate MRAs, which may increase the serum potassium level, in patients with hyperkalemia, chronic kidney disease, and heart failure.

Case Report

Before admission

An 88-year-old woman with hypertension was admitted to the hospital with acute heart failure due to aortic stenosis. She was treated initially with non-invasive positive-pressure ventilation, high-dose intravenous diuretics, and spironolactone. After discharge, 25 mg/day of spironolactone was discontinued due to her persistent hyperkalemia (serum potassium around 5.5 mEq/L). She was then referred to our hospital for further management.

On admission

When presenting to our hospital, her blood pressure was 140/98 mmHg, and her pulse rate was 54/min with medications, including azilsartan 40 mg/day and furosemide 20 mg/

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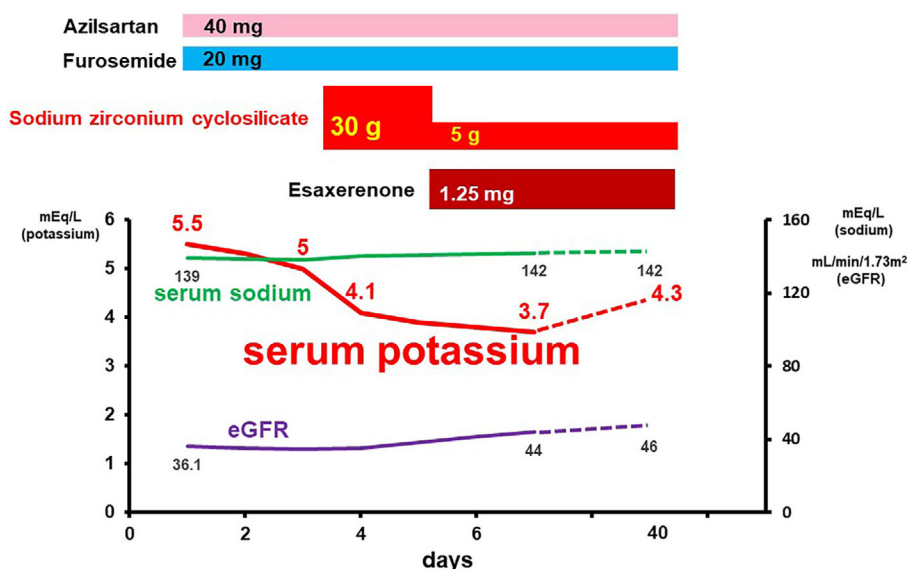


Figure. The clinical course during hospitalization. eGFR: estimated glomerular filtration rate

day. Her serum sodium level was 139 mEq/L, serum potassium was 5.5 mEq/L, estimated glomerular filtration rate was 36.1 mL/min/1.73 m², and plasma B-type natriuretic peptide was 268 pg/mL. Transthoracic echocardiography showed an ejection fraction of 55%, left-ventricular end-diastolic diameter of 44 mm, mild left ventricular hypertrophy, and moderate aortic stenosis with a mean pressure gradient of 34 mmHg.

MRA initiation together with SZC

We considered initiating an MRA again given her resistant hypertension and recurrent heart failure symptoms, despite the presence of persistent hyperkalemia. We hesitated to administer beta-blockers given her bradycardia, and we wished to avoid calcium channel blockers considering her heart failure.

We planned to initiate an MRA following improvement in hyperkalemia after the SZC therapy. We used esaxerenone considering her hypertension and renal impairment. Following the 2-day administration of SZC at a loading dose (30 mg/day), her serum potassium level decreased from 5.0 mEq/L to 3.9 mEq/L (Figure). After confirming the improvement in the serum potassium level, we initiated 1.25 mg/day of esaxerenone together with SZC at a maintenance dose (5 mg/day).

Following confirmation that her laboratory data, including her serum potassium level, had remained stable without recurrence of hyperkalemia, she was discharged transiently with a plan to receive transcatheter aortic valve replacement later. One month later, her serum potassium level was 4.3 mEq/L, estimated glomerular filtration rate was 46 mL/min/1.73 m², and blood pressure was 124/84 mmHg. Following discharge, her serum potassium level remained between 4.0 and 4.5 mEq/L for 3 months. She had no complications following the SZC administration.

Discussion

Hyperkalemia in patients with heart failure

In addition to renin-angiotensin system inhibitors, MRAs are an important treatment option that improve the survival in patients with heart failure and a reduced ejection fraction; furthermore, their efficacy is also likely in those with heart failure and a preserved ejection fraction (1-3). Esaxerenone is the most recently developed MRA and has been proposed as potentially effective in treating patients with hypertensive heart failure (4).

However, these medications may cause clinically significant hyperkalemia, particularly for elderly patients with chronic kidney disease (5, 6). Sustained hyperkalemia is associated with increased mortality among those with heart failure, chronic kidney disease, or both (9). As a result, clinicians sometimes hesitate to administer MRAs, particularly for elderly patients with chronic kidney disease and mild hyperkalemia (approximately serum potassium level between 5.0 and 5.5 mEq/L).

SZC to treat hyperkalemia

SZC is a recently developed non-absorbed, non-polymer zirconium silicate compound that preferentially exchanges hydrogen and sodium for potassium and ammonium ions in the gastrointestinal tract. The HARMONIZE Global trial randomized 267 patients with hyperkalemia into the SZC arm (5 g or 10 g) and the placebo arm. SZC normalized 89.1% of cases of hyperkalemia during the first 48 hours and maintained average serum potassium levels of 4.8 mEq/L (SZC 5 g arm) and 4.4 mEq/L (SZC 10 g arm). There were no significant adverse events associated with SZC during the observational period in their study. We used SZC instead of other conventional potassium chelating agents that

lack concrete evidence concerning their safety and efficacy.

Combination therapy using SZC and MRA

In this patient, we were able to safely initiate esaxerenone without recurrence of hyperkalemia following the confirmation that SZC had normalized the hyperkalemia. The decrease in serum potassium concentration during the 2-day SZC loading therapy was 1.1 mEq/L, which was comparable to the average reduction of 1.28 mEq/L seen in the HARMONIZE Global trial (7). The concomitant administration of SZC might become an established strategy for aggressively but safely administering MRA, particularly in elderly patients with chronic kidney disease and mild hyperkalemia. A similar concept was recently proposed in the United States (10), but few reports have validated or even described this concept. Of note, the applicability of this concept to Japanese patients remains unknown.

However, we should practice caution before making any conclusions without definitive findings from studies; this case report is merely a proof of concept. Further prospective randomized control trials with longer-term observational data are needed in order to investigate the efficacy of SZC on maintaining the serum potassium level in the setting of therapies like MRAs. In addition, we should also take care to ensure that continuous SZC administration does not induce the development of hypokalemia, and the dose of SZC should be adjusted if necessary in order to keep the serum potassium level in the appropriate range. Despite several large-scale trials (2, 3), the clinical implications of MRA add-on therapy in elderly patients with chronic kidney disease remain unclear. This should also be explored in the future.

Conclusion

SZC might be a promising therapeutic tool for safely administering MRA in patients with heart failure and hyperkalemia. Further prospective randomized control trials are warranted to validate the safety and efficacy of combination therapy using SZC and MRAs.

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

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