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CASE REPORT
Heart failure

Use of potassium-binder patiromer for up-titration of renin–angiotensin–aldosterone system inhibition therapy in a patient with chronic heart failure and reduced ejection fraction followed in a multidisciplinary integrated chronic care management programme: a case report

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Background Chronic heart failure (CHF) is a growing epidemic. The cornerstone of pharmacological therapy in CHF patients with reduced ejection fraction (HFrEF) is the inhibition of the renin–angiotensin–aldosterone system (RAAS). One of the adverse effects of RAAS blockade is the development of hyperkalaemia, which often limits the optimization of recommended, Class I treatments. In this context, potassium binders patiromer or sodium zirconium cyclosilicate (ZS-9) provide an opportunity to optimize the pharmacological management of these patients.

Case summary We present a case report illustrating our real-life experience using the potassium-binder patiromer in a patient with HFrEF, in whom recurrent hyperkalaemia (up to 6.3 mmol/L with low doses of enalapril) was preventing titration of RAAS inhibition therapies. Use of patiromer allowed re-introducing ramipril (subsequently switched to sacubitril/valsartan) and eplerenone. Serum potassium levels remained normal with patiromer 16.8 g/24 h, and the patient's tolerance to patiromer was excellent.

Discussion In patients with HFrEF and recurrent hyperkalaemia, optimal RAAS inhibition is often discontinued. In this context, novel potassium binders such as patiromer or ZS-9 have been shown to be effective in lowering potassium and maintaining normokalaemia, with a good safety profile and patient tolerance, all of which make them promising alternative options. Our preliminary experience suggests that patiromer may be a helpful and well-tolerated treatment option, which may aid in achieving optimal RAAS inhibition in HFrEF patients with recurrent hyperkalaemia. Registries of HFrEF patients will help better understand whether therapies such as patiromer have prognostic benefits through facilitating optimal RAAS blockade.

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Keywords Case report • Chronic heart failure • Heart failure • Hyperkalaemia • Patiromer • Potassium

Learning points

- Hyperkalaemia may prevent the optimization of therapy in patients with chronic heart failure (CHF) impacting prognosis.
- Calcium/sodium polystyrene sulphonates, a common treatment to avoid recurrent hyperkalaemia in clinical practice in Europe, has a lack of evidence in its efficacy and is associated with side effects.
- New potassium binders such as patiromer or zirconium cyclosilicate can be an important treatment option to avoid hyperkalaemia in patients with chronic conditions as CHF and chronic kidney disease.

Introduction

Chronic heart failure (CHF) is a growing public health problem.[1] Around half of the patients with CHF have a left ventricular ejection fraction (LVEF) below 40%—so-called 'heart failure with reduced ejection fraction' (HFrEF).[2,3] A major cornerstone of medical therapy in these patients is the inhibition of the renin–angiotensin–aldosterone system (RAAS).[2,3] An undesirable effects of RAAS blockade is the development of hyperkalaemia (defined as serum potassium levels > 5.0 mmol/L),[4] a condition which often prevents optimizing Class I pharmacotherapies such as angiotensin-converting enzyme inhibitors (ACEIs)[5] or mineralocorticoid receptor antagonists (MRAs),[6] a failure which is likely to have prognostic implications.[4]

In this context, novel treatments for hyperkalaemia such as patiromer or sodium zirconium cyclosilicate (ZS-9) provide an opportunity to ameliorate this issue.[4,7,8] These potassium binders have been recently approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) (FDA approval in 2015 and EMA approval in 2017 for patiromer use, and both FDA and EMA approvals for ZS-9 use in 2018).[9] Nevertheless, the real-world experience with these therapies is currently limited.

Timeline

June 2017	Discharge after acute heart failure hospitalization. Follow-up in multidisciplinary chronic care management programme
July 2017	Enalapril 10 mg + eplerenone 25 mg
August 2017	Enalapril + eplerenone discontinuation [Potassium (K+) 6.3 mmol/L]
September 2017	Ramipril 1.25 mg
October 2017	Ramipril discontinuation (K+ 6.1 mmol/L)
November–December 2017	Hospital admission due to acute heart failure
December 2017	Discharge after acute heart failure hospitalization. Ramipril 2.5 mg + patiromer 8.4 g
January 2018	Ramipril 2.5 mg + patiromer 16.8g (K+ 5.4 mmol/L)
February 2018	Ramipril 5 mg + patiromer 16.8 g
March 2018	Ramipril 5 mg + eplerenone 12.5 mg + patiromer 16.8 g
April 2018	Ramipril 5 mg + eplerenone 25 mg + patiromer 16.8 g
May 2018	Ramipril discontinuation
	Sacubitril/valsartan 24/26 mg + eplerenone 25 mg + patiromer 16.8 g

Case presentation

We present a 74-year-old Caucasian male with a history of Type 2 diabetes mellitus, hypertension, hypercholesterolaemia, former tobacco use, chronic pulmonary obstructive disease, and chronic kidney disease (CKD) Stage 3 [baseline estimated glomerular filtration rate (eGFR) ranging 40–50 mL/min]. Relevant cardiac history included atrial fibrillation and ischaemic heart disease with an acute myocardial infarction (AMI) in 2009; the angiography showed coronary disease: chronic total occlusion of the right coronary artery and severe stenosis of the proximal left anterior descending artery, treated percutaneously with a drug-eluting stent.

After the AMI, the patient's LVEF was <40%, and he developed HFrEF. He presented several acute decompensations requiring hospital admissions between 2011 and July 2017. In the latter admission, echocardiography showed a dilated left ventricle (end-diastolic volume: 67 mL/m^2), LVEF 34%, moderate functional mitral regurgitation, normal right ventricle without pulmonary hypertension. A stress echocardiography was performed, showing no ischaemia and no significant worsening of mitral regurgitation. The patient was discharged in a New York Heart Association (NYHA) functional Class IIb, with suboptimal medical therapy.

It was then when the patient began follow-up in the multidisciplinary CHF management programme, which included intensive health education, and careful pharmacological titration. During follow-up, low doses of an ACEI (enalapril), a beta-blocker (nebivolol), and

MRA (eplerenone) were initiated sequentially, as per current clinical practice guidelines.

Up-titration of beta-blockers up to 10 mg/day was successfully achieved after 2 months. The same did not occur with enalapril and eplerenone: both had to be discontinued 2 weeks after initiating eplerenone due to deterioration of renal function and hyperkalaemia (eGFR 30 mL/min, K + 6.3 mmol/L). There were no clinical manifestations, no significant arrhythmias and both T wave and the QRS complex remained unaltered in the electrocardiogram. Blood tests showed a recovery of renal function and potassium levels 1 week after (eGFR 39 mL/min, K + 4.9 mmol/L). A few weeks later, in a second attempt to use ACEIs, low doses of ramipril (1.25 mg/24 h) were initiated. Despite the very low dose, K+ levels raised again up to 6.1 mmol/L (eGFR unchanged). Ramipril was discontinued, and the patient was once again questioned about dietary habits, with no evidence of intake of potassium-rich foods, supplements, or other preventable causes of hyperkalaemia.

To facilitate further attempts to optimally inhibit the RAAS, calcium polystyrene sulphonate was introduced. Nevertheless, the patient spontaneously abandoned treatment due to self-reported gastric intolerance. During this period, the patient suffered a new acute decompensation of CHF in the context of a respiratory infection, leading to acute pulmonary oedema.

Certain that was unable to achieve optimal RAAS inhibition due to recurrent hyperkalaemia, we requested special permission to use patiromer, a potassium binder which had not been commercialized in Europe by then. After discharge (eGFR 50 mL/min, K + 4.6 mmol/L) patiromer 8.4 g/24 h and ramipril 2.5 mg/24 h were initiated simultaneously. The laboratory tests 3 days later showed serum potassium levels of 5.4 mmol/L, eGFR 53 mL/min. Ramipril was maintained, and the dose of patiromer was doubled (16.8 g/24 h); subsequent blood test showed serum potassium levels back to normal (4.9 mmol/L). Ramipril was then up-titrated to 5 mg/24 h, without evidence of hyperkalaemia in the subsequent controls. MRAs were then reintroduced. First, 12.5 mg/24 h of eplerenone, potassium levels being persistently <5 mmol/L, followed by up-titration to 25 mg/24 h. The patient's subjective tolerance was excellent, and blood tests consistently showed stable eGFRs and potassium levels.

Given the persistent NYHA Class IIb, during follow-up, ramipril was replaced by an angiotensin receptor blocker neprilysin inhibitor (sacubitril/valsartan 24/26 mg), with no recurrence of significant hyperkalaemia. There were no substantial differences in renal function or electrolytes before and after patiromer initiation, except potassium levels. Creatinine and eGFR levels ranged 130–150 µmol/L and 40–50 mL/min, respectively, and phosphate levels ranged 1.1–1.2 mmol/L. Magnessemia ranged 0.6–0.7 mmol/L, i.e. compatible with mild hypomagnesemia, which was present before patiromer initiation and was not worsened by therapy. It has not been possible to further up-titrate RAAS inhibitors due to arterial hypotension (persistent asymptomatic systolic blood pressure below 90 mmHg). The patient is now in NYHA Class IIa and has had no recent decompensations.

After 3 months under optimal medical therapy, follow-up echocardiography has recently been performed, showing no significant changes: the left ventricle remained dilated, with an LVEF of 35%. The patient will soon receive an implantable cardioverter-defibrillator.

Discussion

We present a case report illustrating the real-life use of potassium-binder patiromer in a patient with HFrEF and recurrent hyperkalaemia, which precluded optimal RAAS inhibition. In these patients, clinical practice guidelines recommend looking for reversible causes (diet, supplements, drugs) and correcting them.[2–4] Lowering or discontinuation of RAAS inhibitors is recommended when potassium levels are >5.5 mmol/L.[2–4]

Although clinical experience with potassium binders in patients with CHF and CKD is accumulated for calcium/sodium polystyrene sulphonate, clinical trial evidence on its efficacy is lacking and its prolonged use may be associated with severe side effects, such as bowel necrosis.[10,11] Also, patient tolerance is usually poor, mainly due to gastrointestinal symptoms. In this context, novel potassium binders such as patiromer and ZS-9, both of which have been shown to be effective in lowering potassium and maintaining normokalaemia in patients with CHF, CKD, and hyperkalaemia, with a good safety profile and patient tolerance,[7,8] appear as promising alternative options.[12]

Patiromer is an oral non-absorbed polymer, which exchanges calcium and K+ in the colon, resulting in increased K+ excretion. Drug–drug interactions are uncommon, and there are no significant systemic side effects. The most frequent include gastrointestinal symptoms (i.e. diarrhoea, constipation) and non-serious electrolyte abnormalities (i.e. hypomagnesaemia). Sodium zirconium cyclosilicate is an inorganic cation that eliminates excess potassium in the gastrointestinal tract. In clinical trials, the short-term safety profile of ZS-9 seems similar to placebo; studies with longer follow-up are needed. In a recent review of potassium binders among CKD, there were encouraging outcomes in maintaining normokalaemia and RAAS inhibitors in patients with eGFR between 15 and 60 mL/min. There are also some positive real-world data in patients in haemodialysis under patiromer.[11]

Our preliminary experience suggests that patiromer may be a helpful treatment to achieve optimal RAAS inhibition, preventing hyperkalaemia and enabling up-titration of Class IA drugs in CHF patients. Large registries of HFrEF patients will help better characterize the effectiveness of these novel therapies, as well as identify the subgroups of patients most likely to benefit.

Lead author biography

Dr Josep Comín-Colet has born in Barcelona in 1968. Studied Medicine and Surgery in Barcelona University, Internal Medicine Resident in the UK, and Cardiology specialist training at the Hospital of Bellvitge (Barcelona) between 1996 and 2001. Great expertise in Heart Failure, he developed the Heart Failure Program at the Hospital del Mar (University Hospital in Barcelona, Spain). Doctor in Medicine (PhD) at the Autonomous University of Barcelona. Currently,

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Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: J.C.-C. has received speaker fees from Vifor Pharma. All other authors declared no conflict of interest.

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