Management of hyperkalaemia in acute kidney injury in a heart failure patient with patiromer

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Abstract

**Aims** One prevalent comorbidity of chronic heart failure (CHF) is chronic kidney disease (CKD). Hyperkalaemia is associated with both CHF and CKD, which often leads to withdrawal of heart failure medications in clinical praxis.

**Methods and results** A patient is presented who suffered from acute kidney injury with pre-existing CKD as heart failure comorbidity and a history of hyperkalaemia.

**Conclusions** This case shows that potassium levels remained stable in acute kidney injury under ongoing heart failure medications, including an MRA, with the use of the potassium binder patiromer.

Keywords Chronic Heart Failure; Chronic Kidney Failure; Heart Failure Therapy; Hyperkalaemia

Introduction

In chronic heart failure (CHF), chronic kidney disease (CKD) is one of the most prevalent co-morbidities. Patients with CHF and CKD show a worse prognosis than those without CKD. The close interaction of the heart and the kidney was described by the term cardiorenal syndrome (CRS) depending on intra-renal haemodynamics, trans-renal perfusion pressures, and neurohormonal factors. Associated with CRS is the problem of derailment of electrolytes especially a high incidence of hyperkalaemia. The risk of hyperkalaemia in HF is further increased by guideline-recommended drugs improving mortality and morbidity like mineralocorticoid antagonists or renin–angiotensin system inhibitors (RASi). New potassium binders, like patiromer or ZS, have been shown to be effective in the treatment of hyperkalaemia and will be assessed in HF to enable adequately dosed mineralocorticoid receptor antagonists (MRAs), RASI, and sacubitril/valsartan.

Case report

A 69-year-old woman presented with shortness of breath, dizziness, and vomiting in the emergency room. The patient reported not to have drank and eaten for 48 h with limited sleep with consecutive socio-psychological stress owing to grief over the loss of a loved one. According her past medical history, the patient has been suffering from CHF disease due to ischaemic cardiomyopathy with a systolic ejection fraction of 28% at the last visit in the HF clinic. Because of a bradycardia–tachycardia syndrome in connection with atrial fibrillation, a pacemaker was implanted. Because of haemodynamically relevant ventricular tachycardia and reduced ejection fraction before, the pacemaker was upgraded to an implanted cardioverter defibrillator. She was recently discharged after an acute HF decompensation. Before admission, there was an interrogation of implantable cardioverter defibrillator. There was an atrial pacing of 76% with less than 0.1% ventricular pacing with no episodes of ventricular tachycardia or persisting atrial fibrillation detected. The medical treatment at discharge consisted of bisoprolol 5 mg/day, sacubitril/valsartan 24/26 mg, spironolactone 25 mg/day, and 80 mg of torasemide. In addition, peripheral arterial occlusive disease, coronary artery disease, and liver cirrhosis were other relevant comorbidities. The patient was suffering from CKD with daily variations of estimated glomerular filtration rates (eGFR).
equation) between 25 and 40 mL/min/1.73 m². Also according her past medical history, she has been hospitalized recurrently owing to acute-on-chronic kidney failure with consecutive hyperkalaemia. Because even small reductions of renal function in this patient were accompanied by hyperkalaemia episodes with serum potassium up to 6.2 mmol/L previously, therapy with patiromer 8.4 g/day was established after discharge from the previous hospital stay 6 months ago.

Physical examination on admission revealed dry mucosa and standing skin folds. The patient presented with impaired orientation. At hospitalization (Day 1 in Figure 1A–D), lab values showed high creatinine of 3.2 mg/dL, eGFR of 14.1 mL/min/1.73 m², and urea of 242 mg/dL but still normal potassium of 4.0 mmol/L on patiromer. Creatinine and urea concentrations were higher and eGFR significantly lower than the average outpatient values after the previous HF hospitalization, which were also accompanied by impaired renal function. Other electrolytes showed normal values. Electrocardiogram showed sinus rhythm with atrial pacing with intrinsic atrioventricular transition that persisted throughout the hospitalization. The patient was not suffering from palpitations at admission or during hospitalization.

**Therapy**

Upon physical examination, elevated creatinine and urea led to the diagnosis of acute kidney failure due to exsiccosis. Physical examination and medical history were suggestive of volume depletion, but interestingly, potassium concentrations were in the normal range. Therefore, volume was substituted with electrolyte solutions with 2 L in the first 24 h and another 3 L in the subsequent 2 days. Under fluid therapy, creatinine value decreased to 3.0 mg/dL at Day 1 (Figure 1A). Continuing fluid therapy lowered creatinine levels to 1.96 mg/dL corresponding to her former creatinine levels. In parallel, urea levels decreased from 242 to 126 mg/dL (Figure 1C), and creatinine–eGFR levels increased from 15.4 to 35.8 mL/min/1.73 m² (Figure 1B). Serum sodium concentrations decreased from 147 to 136 mmol/L during fluid therapy (Figure 1E). Initially, potassium was at 4.2 mmol/L at a patiromer dose of 8.4 mg twice a day. At the following days, potassium level was kept stable between 3.7 and 4.0 mmol/L (Figure 1D). On Day 5, we were able to up-titrated spironolactone to 50 mg/day (Figure 1D) to intensify HF treatment without rise of potassium. Blood pressure was kept stable between systolic 120 mmHg and...
Hyperkalaemia represents an important clinical problem, because the frequent CRS is associated with impaired potassium excretion and with high mortality. Mortality and morbidity are reduced by guideline-directed MRAs and RASi, although these drugs can lead to or augment life-threatening hyperkalaemias. In clinical practice, physicians often continuously stop or do not up-titrate potassium-retaining drugs like spironolactone despite their benefits on outcomes. A recent study showed that only 54% of hyperkalaemia episodes were directly associated with MRA therapy, while on placebo, hyperkalaemia occurred also in 46%. In consequence, 46% were related to other reasons, but hyperkalaemia workup is often dismissed. The Guidelines of the European Society of Cardiology recommend not only to continuously withdraw but also to intermittently pause renin–angiotensin–aldosterone system (RAAS) inhibitor therapy until the workup of hyperkalaemia is finished. Even though RAAS blockers can frequently cause a decrease in eGFR, the treatment benefit in these patients is maintained.

Pathophysiology of hyperkalaemia involves either extracellular potassium shifts or decreased renal excretion. Approximately 73% of patients with advanced CKD and 40% of HF patients may be at risk of elevating potassium levels. Equivalent to reasons, treatment of hyperkalaemia consists either of shifting potassium into cells via insulin/glucose, with beta-agonists activating the Na⁺-K⁺ ATPase or sodium bicarbonate. The other approach consists of elimination of potassium from the body by diuretic therapy or haemodialysis. A new approach for suppressing hyperkalaemia in CKD and HF is the potassium binder patiromer. The active moiety of patiromer is a non-absorbable oral K⁺-binding polymer that primarily acts in the distal colon to increase faecal K⁺ excretion.

In the OPAL-HK study, 2015 patients with CKD on RAAS inhibitor medication were randomized to patiromer or placebo. Patiromer lowered mean serum K⁺ compared with placebo and also reduced the number of patients with recurrent hyperkalaemia, allowing significantly more patients to remain on RAAS inhibitor therapy. In the case presented here, there was an impressive dissociation of creatinine and urea concentrations and potassium levels on patiromer in acute kidney injury, even though this patient had regular episodes of hyperkalaemia before as reason to treat her with patiromer and include her in an observational patiromer study (CONTINUE-HF NIS, DRKS-ID: DRKS00014825).

Effective treatment of arterial hypertension is essential to prevent patients from developing CHF and CKD. According to European Society of Cardiology (ESC) Guidelines for the treatment of hypertension, spironolactone is recommended for patients with uncontrolled, resistant hypertension. The AMBER trial evaluated whether the use of patiromer allows persistent use of spironolactone in patients with CKD and resistant hypertension. More patients (86% vs. 66%) on patiromer therapy were able to continue treatment with spironolactone with less hyperkalaemia as compared with those on placebo.

One might ask why this patient suffered from acute kidney injury. The patient was discharged after an acute decompensation from the hospital. On admission, the patient presented with generalized oedema and was recompensated with diuretics, and sacubitril/valsartan was added to the discharge medication together with diuretics. Sacubitril/valsartan reduces diuretic demand in the PARADIGM trial and in real-life conditions, when patients are being treated by their family physicians owing to haemodynamic intrarenal and natriuretic effects of the drug. Therefore, the reduced fluid intake due to psychosocial stress as well the reduced diuretic demand under sacubitril/valsartan at high diuretic discharge doses probably might have caused acute kidney injury in this patient.

Taken together, this case study shows that potassium levels can be kept stable even in acute kidney failure and ongoing HF medications and even in a patient with previous hyperkalaemia with the use of potassium binder patiromer.

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Conflict of interest

J. S., I. K., and J. D. have nothing to declare. M. B. received consulting honoraria from Vifor and is the chairman of CONTINUE-HF.

References

1. Silverberg D, Wexler D, Blum M, Schwartz D, Laina A. The association between congestive heart failure and chronic renal disease. *Curr Opin Nephrol Hypertens* 2004; 13: 163–170.
2. Hamaguchi S, Tsuchihashi-Makaya M, Kinugawa S, Yokota T, Ide T, Takeshita A, Tsutsui H, The JCARE-CARD Investigators. Chronic kidney disease as an independent risk for long-term adverse outcomes in patients hospitalized with heart failure in Japan: Report from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). *Circ J* 2009; 73: 1442–1447.
3. Iwanaga Y, Miyazaki S. Heart failure, chronic kidney disease, and biomarkers—an integrated viewpoint. Circ J 2010; 74: 1274–1282.

4. Dolovich L, Gavura S, Pottie K. Hyperkalemia associated with spironolactone therapy. Can Fam Physician 2005; 51: 357–360.

5. Bushinsky DA, Williams GH, Pitt B, Freeman MW, Garza D, Stasiv Y, Li E, Berman L, Bakris GL. Patiromer induces rapid and sustained potassium lowering in patients with chronic kidney disease and hyperkalemia. Kidney Int 2015; 88: 1427–1433.

6. Anker SD, Kosiborod M, Zannad F, Piña IL, McCullough PA, Filippatos G, van der Meer P, Ponikowski P, Rasmussen HS, Lavin PT, Singh B, Yang A, Deedwania P. Maintenance of serum potassium with sodium zirconium cyclosilicate (ZS-9) in heart failure patients: results from a phase 3 randomized, double-blind, placebo-controlled trial. Eur J Heart Fail 2015; 17: 1050–1056.

7. Pitt B, Anker SD, Bushinsky DA, Kitzman DW, Zannad F, Huang IZ. PEARL-HF Investigators. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. Eur J Heart Fail 2011; 32: 820–828.

8. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, van Lente F, Greene T, Coresh J. CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150: 604–612.

9. Ueda Y, Ookawara S, Ito K, Miyazawa H, Kaku Y, Hoshino T, Tabie K, Morishita Y. Changes in urinary potassium excretion in patients with chronic kidney disease. Kidney Res Clin Pract 2016; 35: 78e83.

10. Lassus J, Harjola VP, Sund R, Stiilil-Waris K, Melin J, Peukuriinien K, Pulikki K, Nieminen MS, FINN-AKVA Study group. Prognostic value of cystatin C in acute heart failure in relation to other markers of renal function and NT-proBNP. Eur J Heart J 2007; 28: 1841–1847.

11. Juurlink DN, Mandani MM, Lee DS, Kopp A, Austin PC, Laupacis A, Redelmeier DA. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med 2004; 351: 543–551.

12. House A. Management of heart failure in advancing CKD: core curriculum 2018. Am J Kidney Dis 2018; 72: 284–295.

13. Vukadinović D, Lavall D, Nikolovska-Vukadinovic A, Pitt B, Wagenknecht S, Böhm M. True rate of mineralocorticoid receptor antagonists-related hyperkalemia in placebo-controlled trials: a meta-analysis. Am Heart J 2017; 188: 99–108.

14. Pitt B, Rossignol P. Serum potassium in patients with chronic heart failure: once we make a U-turn where should we go? Eur J Heart Fail 2017; 38: 2897–2899.

15. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, Gonzalez-Juanatey JR, Harila VP, Jankoska EA, Jøssup M, Linde C, Nihoyannopoulos P, Parissis JT, Pie ske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force Members, Document Reviewers. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016; 18: 995–1051.

16. Rosano GMC, Tamargo J, Kjeldsen KP, Lainscak M, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfood F, Re don J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shiyakhto E, Tsiofis C, Aboyans V, Desormais I. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur J Heart Fail 2018; 39: 3021–3104.

17. Gayaral R, Rossignol P, Romero A, Garza D, Mayo MR, Warren S, Ma J, White WB, Williams B. Patiromer versus placebo to enable spironolactone use in patients with resistant hypertension and chronic kidney disease (AMBER): a phase 2, randomized, double-blind, placebo-controlled trial. Lancet 2019; 394: 1540–1550.

18. Vardeny O, Claggett B, Kachadoorian J, Desai AS, Packer M, Rouleau J, Zile MR, Swedberg K, Lefkowitz M, Shi V, McMurray JJV, Solomon SD. Reduced loop diuretic use in patients taking sacubitril/valsartan compared with enalapril: the PARADIGM-HF trial. Eur J Heart Fail 2019; 21: 337–341.

19. Wachter R, Fonseca AF, Balas B, Kap E, Engelhard J, Schlienger R, Klebs S, Wirsa SB, Kostev K. Real-world treatment patterns of sacubitril/valsartan: a longitudinal cohort study in Germany. Eur J Heart Fail 2019; 21: 588–597.

20. Boerigger G, Burnett JC Jr. Recent advances in natriuretic peptides in congestive heart failure. Expert Opin Investig Drugs 2004; 13: 643–652.

21. Kobori H, Mori H, Masaki T, Nishiyama A. Angiotensin II blockade and renal protection. Curr Pharm Des 2013; 19: 3033–3042.