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New treatments for hyperkalaemia: clinical use in cardiology

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Hyperkalaemia causes significant burden, and even mild hyperkalaemia has been independently associated with increased morbidity and mortality. Patients with chronic disease states, such as heart failure, hypertension, chronic kidney disease and diabetes mellitus, are increasingly susceptible to the development of hyperkalaemia. Options for management of hyperkalaemia had mainly been limited to short-term, temporizing methods with focus on rapid achievement of normokalaemia. Until recently, there was a lack of safe, efficacious and well-tolerated therapies for long-term management. Two novel potassium binders, patiromer and sodium zirconium cyclosilicate, have recently been approved by the US Food and Drug Administration for the management of hyperkalaemia. This review discusses these potassium binders with focus largely on the clinical implications of these agents in patients with chronic cardiovascular conditions.

Introduction

Hyperkalaemia can be a life-threatening condition and is associated with increased risk of all-cause mortality as well as malignant arrhythmias.[1] Patients at highest risk of hyperkalaemia include those with chronic kidney disease (CKD), heart failure (HF), diabetes mellitus (DM), and those on concomitant renin-angiotensin-aldosterone system inhibitor (RAASi) therapy.[1-3] Due to increasing prevalence of these chronic disease states, development of both acute and chronic hyperkalaemia is more commonly encountered in clinical practice.[4] Development of hyperkalaemia often leads to discontinuation or dose-reduction of RAASi, including mineralocorticoid receptor antagonists (MRAs).[1,5] However, these therapies reduce morbidity and mortality risk in patients with HF with reduced ejection fraction across the spectrum of symptoms and possibly reduce HF hospitalization risk in patients with HF with preserved ejection fraction.[6-10] Therefore, suboptimal dosing or discontinuation places patients at increased risk of adverse events, including death. Clinicians face the challenge of finding a balance between optimizing life-saving therapy and minimizing hyperkalaemia-associated risk. Although acute, temporizing measures for rapidly lowering serum potassium concentration and stabilizing cell membranes are successful, current treatment options for chronic hyperkalaemia are highly limited by lack of effective agents.[11] Loop diuretics are sometimes considered for chronic management of hyperkalaemia but can lead to worsening renal function, volume contraction, and diuretic resistance, and increased long term use has been associated with increased cardiovascular mortality in patients with HF.[12-14] Thus, long-term management of hyperkalaemia has largely been limited to the potassium binder sodium polystyrene sulfonate (SPS), an agent whose use is restricted by uncertain efficacy, poor tolerability, and a side effect profile that includes colonic necrosis,[15-18] believed to be secondary to the sorbitol administered with SPS. Furthermore, the cation exchanged for potassium in SPS, sodium, is retained in the body and can lead to volume retention

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Table 1 Comparison of all Food and Drug Administration approved potassium binders for the long-term management of hyperkalemia

	SPS (Kayexalate)	Patiromer (Veltessa)	SZC (Lokelma)
FDA approval	1958	2015	2018
Mechanism	Non-specific organic ion-exchange resin and exchanges sodium for potassium[16]	Non-specific organic ion-exchange resin and exchanges calcium for potassium[23]	Selective inorganic non-polymer, exchanges sodium, and hydrogen for potassium[24]
Location	Colon[16]	Colon[23]	Throughout gastrointestinal tract[26]
Onset of action	Variable (hours to days)[15]	Within 7 h[25]	Median time 2.2 h[26]
Adverse events	Mild to moderate gastrointestinal effects, variable effects, poor tolerability, electrolyte abnormalities, and colonic necrosis[17,18]	Mild to moderate gastrointestinal effects, hypomagnesaemia, hypokalaemia (3–5.6%)[25,27,28]	Mild to moderate gastrointestinal effects, oedema, and hypokalaemia (0–11% developed hypokalaemia, dose dependent)[26,29]

SPS: sodium polystyrene sulfonate; SZC: sodium zirconium cyclosilicate.

or hypertension, making it a poor choice in patients with chronic diseases with propensity for oedema.[19] There is a compelling need for effective, safe, well-tolerated therapies for the chronic management of hyperkalaemia, a need that may have been satisfied by the development of two novel agents.

Emerging therapies for management of hyperkalaemia

Given the limited armamentarium of therapies available, two novel potassium binders, patiromer (patiromer sorbitex calcium/RLY5016; Veltessa; Relypsa, Red Wood City, CA, USA) and sodium zirconium cyclosilicate (SZC) (Lokelma; AstraZeneca, Wilmington, DE, USA), have been developed and recently approved by the US Food and Drug Administration (FDA) for hyperkalaemia management.[20,21] These agents enhance potassium removal by exchanging cations (calcium for patiromer and sodium for SZC) for potassium in the distal colon, thereby increasing faecal excretion of potassium.[21,22] These agents offer promise in facilitating maintenance of RAASi therapy in patients at high risk for chronic hyperkalaemia who are on suboptimal therapy. Here, we briefly review the clinical trial evidence behind the efficacy and safety profiles of these two agents and focus largely on how these therapies may be used clinically within cardiology. In *Table 1*, we compare the various potassium binders now available for use for chronic hyperkalaemia management.

Patiromer

Patiromer is an organic, non-absorbed polymer that increases faecal excretion of potassium by exchanging it for calcium through the gastrointestinal tract, reaching full ionization in the distal colon to optimize exchange in the region where potassium concentration is greatest.[23] Using calcium (as opposed to sodium) as the counter-ion makes it a more optimal choice in patients with HF and CKD to avoid volume overload and hypertension.[19] Patiromer is also formulated in sorbitol, but the content is significantly lower than that of SPS.[30] The recommended starting dose is 8.4 g per day, which can be up-titrated in 1 week or greater intervals by 8.4 g at a time to maximum dose 25.2 g per day.[25] The FDA approved patiromer in October 2015 for treatment of non-emergent hyperkalaemia.

Clinical trial evidence

The PEARL-HF (Evaluation of Patiromer in Heart Failure Patients) trial investigated patiromer in 105 patients with chronic HF with normal serum potassium (K) levels with either CKD, with an estimated glomerular filtration rate (eGFR) <60 mL/min, or those with a history of hyperkalaemia causing discontinuation of RAASi or beta-adrenergic blocking agents.[31] These patients were initiated on spironolactone in addition to either patiromer or placebo for 4 weeks. Compared with the placebo group, fewer patients who received patiromer developed hyperkalaemia, and more patients who received patiromer were able to increase their spironolactone dose from 25 mg/day to 50 mg/day. Common adverse events were mainly gastrointestinal, and included flatulence, diarrhoea, constipation, and vomiting. Hypokalaemia (serum K <3.5 mmol/L) was observed in 6% of patiromer-treated patients and 0% of placebo-treated patients. Hypomagnesaemia occurred in 24% of patients treated with patiromer vs. 5% of patients treated with placebo.[31]

The AMETHYST-DN (Patiromer in the Treatment of Hyperkalaemia in Patients with Hypertension and Diabetic Nephropathy) studied patiromer in 306 patients with hyperkalaemia (serum K >5.0 mmol/L), Type 2 DM, and CKD with eGFR 15–59 mL/min/1.73 m^2 on prior RAASi therapy.[27] Among these patients, treatment with patiromer led to decreased serum potassium levels after 4 weeks of treatment, maintained up to 52 weeks.

The OPAL-HK (Study Evaluating the Efficacy and Safety of Patiromer for the Treatment of Hyperkalaemia), a two-part study, randomized patiromer in 237 patients with hyperkalaemia (serum K 5.1–6.4 mmol/L) and CKD

on at least one RAASi.[30] The initial part of treatment phase of the study lasted 4 weeks in which patients received varied doses of patiromer. The second portion of the study (8-week withdrawal phase) randomized patients to either continue the initial dose or switch to placebo. Patiromer treatment was associated with a decrease in potassium levels as well as reduction in the recurrence of hyperkalaemia, allowing patients to maintain RAASi therapy. A pre-specified analysis of OPAL-HK evaluated CKD patients with concomitant HF.[28] At the end of the 4-week initial treatment phase, 76% of patients achieved normokalaemia (serum K 3.8–5 mmol/L). By the end of 8 weeks, 52% of placebo patients and 11% of patiromer patients required intervention to manage recurrent hyperkalaemia.[28] A pooled analysis of Phases II and III trials across 666 patients showed the most common side effects of patiromer were constipation (7.2%), hypomagnesaemia (5.2%), diarrhoea (4.8%), nausea (2.3%), abdominal discomfort (2.0%), and flatulence (2.0%).[25] Patiromer can bind to many different oral medications and decrease their effectiveness, so these medications should be given either 6 h before or after patiromer administration.[19]

Sodium zirconium cyclosilicate

Sodium zirconium cyclosilicate is an inorganic, insoluble, and selective cation that preferentially exchanges potassium for sodium and hydrogen, thereby entrapping potassium in the intestine. This agent has very recently been approved (18 May 2018) for non-emergent treatment of hyperkalaemia.[29] Structurally, it is comprised of a lattice framework of oxygen, zirconium, and silicon atoms. With channels that filter ions based on their size, the chemical composition of SZC makes the agent highly selective for potassium cations.[24] Sodium zirconium cyclosilicate acts throughout the gastrointestinal tract. Initial dosing is 10 g three times daily for up to 48 h. Following this, a maintenance dose of 5–15 g administered once daily should be used for continued treatment.[29]

Clinical trial evidence

A short-term Phase II clinical trial (ZS-002) tested SZC in 90 patients with hyperkalaemia (serum K 5.0–6.0 mmol/L) and stable Stage 3 CKD studied over a 2-day period.[32] This study found a significant decrease in serum potassium levels and found SZC to be well tolerated in this patient population.

The ZS-003 trial was a multicentre, Phase III trial that randomly assigned 753 ambulatory patients with hyperkalaemia (serum K 5.0–6.5 mmol/L) to receive either SZC or placebo three times daily for 48 h. Those with normokalaemia following this (serum K 3.5–4.9 mmol/L) were then randomly assigned to SZC vs. placebo for a maintenance phase of 3–14 days. This trial found a rapid, dose-dependent decrease in serum potassium levels over 48 h, which was maintained over 14 days. Rates of adverse events were similar between the placebo and SZC groups, with diarrhoea being the most common adverse event.[33]

The Hyperkalaemia Randomized Intervention Multidose SZC Maintenance (HARMONIZE) study was a Phase III trial analysing SZC in 258 patients with hyperkalaemia (serum K $\geq$5.0 mmol/L). This trial also included an initial 48 h phase, with patients who achieved normokalaemia within 48 h enrolled in a maintenance phase of 28 days.[26] In the HARMONIZE trial, normokalaemia was rapidly achieved (median time to normalization 2.2 h) in the SZC group compared with placebo, and a higher proportion of patients in the SZC group maintained normokalaemia for up to 28 days. Sodium zirconium cyclosilicate was also noted to have a favourable safety and tolerability profile. A further subgroup analysis of the 94 HF patients enrolled in the HARMONIZE trial showed that all three doses of SZC resulted in rapid and sustained normokalaemia in patients with HF, including those on RAASi, thereby preventing dose adjustment of RAASi therapy.[34] It was also noted that the safety profile of SZC in HF patients was similar to that of the overall study population. Adverse events reported in these clinical trials included oedema and hypokalaemia, both mostly seen in patients on higher doses of SZC.[35] To fully ascertain the effect of SZC on oedema, subsequent trials need further information including dietary differences and concomitant diuretic therapy between study populations.[19]

Ongoing studies include ZS005, which has been designed to evaluate the efficacy, tolerability, and safety of SZC for an initial phase of 72 h and a long-term maintenance phase of up to 12 months (NCT02163499). Interim results, presented at the American Society of Nephrology's (ASN) Kidney Week 2017, showed SZC rapidly achieved normokalaemia and maintained these serum potassium levels for up to 12 months.[36]

Role of novel potassium binders in cardiology

Many patients with chronic cardiovascular conditions are at increased risk for developing hyperkalaemia, a condition that puts patients at increased mortality and morbidity risk, and its prevention remains a major treatment goal. Until recently, the only available options were either highly transient or lacked efficacy, with development of hyperkalaemia in chronic conditions often leading to dose alteration of life-saving pharmacologic therapies. The recent FDA approval of both patiromer and SZC for use for treatment of chronic hyperkalaemia has favourable clinical implications in high-risk cardiovascular patients.

Role in heart failure

Chronic HF management has substantially developed over the past few decades, with new treatments offering considerable benefit. Renin-angiotensin-aldosterone system inhibitor therapy, including angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors, and MRAs, is now fundamental in the treatment of HF with reduced ejection fraction, offering proven mortality and morbidity benefit in this population.[6,8,37,38] The American College of Cardiology (ACC)/American Heart Association (AHA)/Heart

Failure Society of America (HFSA) as well as the European Society of Cardiology (ESC) give a Class I recommendation for use of these agents in patients with HF with reduced ejection fraction.[39,40] However, current HF treatment with RAASi puts patients at increased risk of hyperkalaemia.[41]

The pathophysiology behind hyperkalaemia in patients with HF is two-fold. Renal elimination of potassium is promoted by the renin-angiotensin-aldosterone system by means of aldosterone-receptor activation.[1,41–43] Renin-angiotensin-aldosterone system inhibitor interfere with this process, thus impairing renal potassium excretion and inducing or exacerbating hyperkalaemia. Decreased sodium concentrations in the distal convoluted tubule can also lead to hyperkalaemia. With more advanced HF, there is substantial decrease in renal perfusion and consequential increase in proximal reabsorption of sodium. As a result, the concentration of intraluminal sodium in the distal nephron decreases, and this lack of availability can impair potassium secretion.[1,41,44] Concomitant diseases affecting ability to excrete potassium, such as diseases affecting renal parenchyma, further exacerbate hyperkalaemia.[21] These comorbidities include CKD and DM with nephropathy.[2,45–47]

Patients with hyperkalaemia and those with advanced CKD have largely been excluded from participation in large-scale RAASi randomized clinical trials.[6,8,38,48,49] This creates large discrepancy between trial populations and clinical practice, where patients with advanced HF and left ventricular dysfunction who would most benefit from RAASi therapy also have comorbid CKD and increased risk of hyperkalaemia. In clinical practice, prevalence of hyperkalaemia in patients with HF is significantly higher than in trial populations, with highest rates in elderly patients with CKD and on RAASi treatment.[50–55] The clinical significance of hyperkalaemia is being increasingly studied.[56] A growing body of evidence has recently identified higher morbidity and mortality rates in patients with even mild hyperkalaemia, defined as a serum K >5–5.5 mmol/L.[2,57–62] This may be a result of multiple factors including fatal cardiac arrhythmias, comorbidity burden, and underutilization of optimal therapy.[63] Comorbidities including DM2, CKD, cachexia, and sarcopenia can worsen the burden of HF.[64–66] Cachexia and sarcopenia, in particular, can lead to frailty and cause further deterioration in an already aging HF population.[67–71] The development of hyperkalaemia in patients with HF on RAASi therapy often leads to dose reduction to suboptimal levels or complete discontinuation, which prevents vulnerable HF patients from gaining maximal benefit from this lifesaving therapy.[72–74]

With the introduction of novel potassium binders such as patiromer and SZC, patients with HF with or without other comorbidities could potentially have an effective, safe, well-tolerated and long-lasting means of potassium reduction, and maintenance of normokalaemia. This is of particular interest to patients on RAASi therapy. Patiromer and SZC may allow for patients who develop hyperkalaemia to maintain RAASi on optimal doses, offering a morbidity and mortality benefit.[19,75] This may even expand the use of RAASi treatment to patients with HF and advanced CKD (eGFR <30 mL/min), who currently cannot use RAASi.[39,40] An ESC expert consensus document on management of hyperkalaemia in patients with cardiovascular disease on RAASi was recently published, recommending up-titration of RAASi to target dose whenever possible, with co-administration and maintenance therapy with an approved potassium-lowering agent when serum K >5 mmol/L (unless an alternative treatable aetiology of hyperkalaemia is identified).[76] In OPAL-HK, serum aldosterone levels were reduced after 4 and 8 weeks of patiromer use.[30] Reduction in serum aldosterone levels may contribute to reducing hyperkalaemia in patients on RAASi, since RAASi cause hyperkalaemia through inhibition of aldosterone-receptor.[1] However, further clinical trial data are required to ascertain the long-term efficacy, safety and tolerability of patiromer, and SZC for the specific purpose of optimizing RAASi use in patients with HF with and without other comorbidities (such as advanced CKD).

Role in hypertension

Resistant hypertension, or blood pressure over target goal despite use of three agents (usually a calcium channel blocker, ACEi or ARB, and a thiazide-like diuretic), is encountered in up to 10–20% of the general hypertensive population.[77] The presence of resistant hypertension portends a poorer prognosis.[77] Multiple studies have demonstrated the benefit of MRAs in patients with resistant hypertension,[78–83] and they are recommended by guidelines for use as a fourth agent in these patients.[84] However, development of hyperkalaemia leads to discontinuation or dose-reduction of MRA therapy, leaving patients with suboptimal blood pressure control. Continuation of optimal MRA doses are vital in this population, especially given convincing evidence that intensive blood pressure control leads to significantly improved outcomes, guiding recent changes in recommendations for blood pressure control.[84,85]

The recently approved potassium binders may enable use of MRA (and simultaneous use of ACEi or ARB antihypertensive therapy) in patients with resistant hypertension by attaining and maintaining normokalaemia. A recent post-hoc analysis of the AMETHYST-DN study of patients with resistant hypertension with diabetic kidney disease and hyperkalaemia concluded that patiromer effectively controlled hyperkalaemia through a 52-week period, permitting these patients to continue RAASi therapy for adequate blood pressure control.[86] Prospective data to further explore these findings and evaluate the role of potassium bindings in facilitating ACEi or ARB and MRA therapy in resistant hypertension are needed.

Future directions

The development of hyperkalaemia serves as an important juncture in the progression of cardiovascular disease (including HF and hypertension), indicative of a worsening clinical course with increased risk of mortality and hospitalizations. Once it develops, the management of hyperkalaemia has, until recently, remained largely unchanged, with focus on acute management and lack of safe and efficacious methods for long-term management. The

development of hyperkalaemia is also a barrier to RAASi therapy, leading to dose-reduction or discontinuation of these agents. Patiromer and SZC represent significant advancements in our management of hyperkalaemia in chronic cardiovascular conditions. These agents have better efficacy, predictability, tolerability, and safety than the previously available potassium binder, SPS. These new potassium-lowering agents serve as promising additions to the future of HF and hypertension therapy by potentially allowing for the maintenance and optimization of RAASi therapy. Future studies should continue to elucidate the role of these potassium binders in improving long-term clinical outcomes through RAASi optimization across a spectrum of cardiovascular disease.

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