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Pharmacology of new treatments for hyperkalaemia: patiromer and sodium zirconium cyclosilicate

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Hyperkalaemia is a life-threatening condition, resulting from decreased renal function or dysfunctional homoeostatic mechanisms, often affecting patients with cardiovascular (CV) disease. Drugs such as renin-angiotensin-aldosterone system inhibitors (RAASi) are known to improve outcomes in CV patients but can also cause drug-induced hyperkalaemia. New therapeutic options exist to enhance potassium excretion in these patients. To this aim, we reviewed pharmacological properties and available data on patiromer and sodium zirconium cyclosilicate for the treatment of hyperkalaemia. These agents have been shown in randomized trials to significantly reduce serum potassium in patients with hyperkalaemia on renin-angiotensin-aldosterone system inhibitors. Additional research should focus on their long-term effects/safety profiles and drug–drug interactions.

Introduction

Hyperkalaemia, i.e. serum potassium concentrations above 5.0 mEq/L, is a very common condition in cardiovascular (CV) patients, resulting from different causes such as increased potassium intake, impaired distribution between the intracellular and extracellular spaces, and/or reduced renal excretion.[1] Hyperkalaemia is particularly prevalent in patients older than 65 years with advanced chronic kidney disease (CKD), diabetes, and/or chronic heart failure.[2] Of note, elevation in potassium may be induced by drugs that modulate potassium excretion such as angiotensin-converting enzyme inhibitors, renin-angiotensin-aldosterone system inhibitors (RAASi), beta-adrenergic receptor antagonists; angiotensin receptor blockers; mineralocorticoid receptor antagonists.[3] In clinical practice, hyperkalaemia is a crucial limitation to fully titrate RAASi.[4]

Patients with severe hyperkalaemia are at higher risk of mortality, as it may lead to abnormalities in cardiac depolarisation/repolarisation and contractility, resulting in cardiac arrhythmias, and ultimately to sudden cardiac death.[2] To avoid these severe outcomes, treatment for lowering potassium levels should be initiated as early as possible.[5]

Taking into account these issues, here, we summarize the interventions able to improve hyperkalaemia with a particular focus on new treatments such as patiromer and sodium zirconium cyclosilicate (SZC).

Current therapies for hyperkalaemia

Pharmacological characteristics of treatments for hyperkalaemia according to current guidelines[6–8] are summarized in *Table 1*. Briefly, management of acute hyperkalaemia includes reducing dietary potassium and withdrawal of exacerbating drugs; administration of intravenous calcium gluconate, insulin, and glucose; nebulized albuterol; correction of acidosis with sodium bicarbonate to transfer potassium into the cells.[5] Loop diuretics and potassium binders, i.e. sodium polystyrene sulfonate (SPS) and

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Table 1 Pharmacology of current treatments for hyperkalaemia

	Mechanism of action	Adverse effects
SPS/CPS	Removal Onset: 60–180 min Duration: 240–360 K^+ reduction: 0.5–1.0 per 1 g resin	Nausea, constipation, diarrhoea, paralytic ileus, cecal perforation, hypercalcaemia, hypernatraemia
Haemodialysis	Removal Onset: <10 min Duration: <60–180 K^+ reduction : 1.2–1.5/h	Hypokalaemia, arrhythmias
Loop diuretic (furosemide)	Removal Onset: immediate 15 min Duration: 120–180	Ototoxicity, hypokalaemia, nephrotoxicity
Insulin + dextrose	Translocation Onset: <15–30 min Duration: 240–360 K^+ reduction: 0.5–1.5 mEq/L (dose-dependent)	Hypoglycaemia, hyperosmolarity, volume overload
Beta-adrenergic agonists	Translocation Onset: 3–5 min onset Duration: 1–4 h K^+ reduction: 1.6–1.7/2 h (salbutamol)	Tremor, tachycardia
Sodium bicarbonate (only in patients with metabolic acidosis—bicarbonate <22 mEq/L)	Translocation (doubt effect) Correction of acidosis Onset: 30–60 min (onset). Duration: 2–6 h	Hypernatraemia, volume overload, tetany, hypertension
Calcium gluconate	Translocation Stabilise myocardium, protect cardiomycytes Onset: 1–3 min Duration: 30–60 min K^+ reduction: 0.5–1.5 mEq/L	Hypercalcaemia, tissue necrosis

CPS, calcium polystyrene sulfonate; K^+, potassium; SPS, sodium polystyrene sulfonate.

calcium polystyrene sulfonate (CPS) can be used to promote the excretion via renal or gastrointestinal route, respectively. If all these measures are ineffective, haemodialysis may be needed.

Unfortunately, these treatments present some limitations. The use of SPS and CPS is often associated with adverse effects and their efficacy is uncertain.[9,10] Other treatments, i.e. insulin/dextrose and beta-receptor agonists like salbutamol, are not yet approved in some EU countries and present several limitations as well. In particular, their effects are transient and rebound hyperkalaemia can occur after 2 h.[5]

The management of chronic hyperkalaemia poses further challenge. Adverse gastrointestinal effects makes long-term administration difficult. Further, dietary restrictions must be maintained over time, and long-term cessation of potassium retaining agents is detrimental on CV/renal outcomes.[5] The ESC heart failure guidelines recommend that if a withdrawal of these drugs is needed, it should be kept at minimum, and RAASi should be cautiously re-established as soon as possible while monitoring potassium levels.[11]

Considering all these limitations, new therapeutic options for the chronic management of patients with hyperkalaemia are warranted. To this aim, oral therapies such as patiromer calcium and SZC have been recently developed.

New treatments for hyperkalaemia: patiromer calcium and sodium zirconium cyclosilicate

Patiromer calcium and SZC are two new polymer-based, non-systemic agents formulated to increase potassium reduction via the gastrointestinal tract. *Table 2* compares their pharmacodynamic and pharmacokinetic properties.

Patiromer

Pharmacological properties and available data

Patiromer is an oral potassium binder, a novel next-generation spherical non-absorbed polymer, recently approved by the FDA for the treatment of chronic hyperkalaemia.

Its mechanism of action has been described in detail elsewhere.[12] Briefly, the patiromer polymer has a low molecular weight, providing a higher absolute binding capacity. Also, patiromer is characterized by a minimal water absorption and the exchange cation involves calcium and not sodium.[13] For this reason, it is a preferable choice for

Table 2 Pharmacodynamics and pharmacokinetics of sodium zirconium cyclosilicate and patiromer

	SZC	Patiromer
Form	Powder for oral suspension: 5 g/sachet 10 g/sachet	Powder for oral suspension: 8.4 g/packet 16.8 g/packet 25.2 g/packet
Dosage	Initial: 10 g PO TID for up to 48 h Maintenance: 5 g to 10 g PO once daily or 5 g every other day	Initial: 8.4 g PO qDay Maintenance: may increase or decrease dose as necessary; not to exceed 25.2 g qDay May be uptitrated upwards at 1 week or longer intervals, in increments of 8.4 g Doses exceeding 50.4 g/day have not been tested; excessive doses may result in hypokalaemia; restore serum potassium if hypokalaemia occurs
Adverse effects	Oedema (6%) Hypokalaemia (4%)	Constipation (7.2%) Hypomagnesaemia (5.3%) Diarrhea (4.8%) Hypokalaemia, <3.5 mEq/L (4.7%) Nausea (2.3%) Abdominal discomfort (2%) Flatulence (2%)
Mechanism of action	Potassium binder and remover Captures and removes potassium from the GI tract Increases faecal potassium excretion	Potassium binder Removal. Binds and removes potassium from the GI tract, particularly the colon Increases faecal potassium excretion
Contraindications/cautions	Avoid with severe constipation or bowel obstruction or impaction, including abnormal post-operative bowel motility disorders Drug interactions: transient increase in gastric pH	Avoid with severe constipation or bowel obstruction or impaction, including abnormal postoperative bowel motility disorders Monitor for hypomagnesemia Patiromer binds many orally administered medications
Limitations	Not to be used as an emergency treatment for life-threatening hyperkalaemia because of its delayed onset of action	Not to be used as an emergency treatment for life-threatening hyperkalaemia because of its delayed onset of action
Absorption	Not systemically absorbed	Not systemically absorbed
Elimination	Excretion: faeces	Excretion: faeces

GI, gastrointestinal; PO, per os (per mouth); qDay, one a day; TID, three times a day.
Data from FDA-approved labelling information.

patients who cannot tolerate even small increases in sodium load. A study[12] showed that patiromer is not systemically absorbed, also demonstrating its lack of systemic bioavailability. In particular, patiromer is fully ionized at the physiological pH of the colon, where the concentration of potassium in the gastrointestinal tract is the highest, thus providing optimal ion exchange. It decreases serum potassium via an increase in faecal excretion. In a Phase 1 study on 33 healthy participants,[12] patiromer increased faecal and decreased urinary potassium excretion, remaining physically stable during passage through the gastrointestinal tract. The fact that the patiromer polymer is not absorbed is a major contributing factor for its safety profile (see below).[14]

Three main clinical trials (PEARL-HF,[15] OPAL-HK,[16] and AMETHYST-DN[17]) examined the safety and efficacy of patiromer in patients with hyperkalaemia as summarized in *Table 3*. All three studies achieved their primary endpoints and reduced serum potassium in patients with CKD, Type 2 diabetes mellitus, hypertension, and/or heart failure. Thus, available data collected so far show patiromer to be effective in decreasing serum potassium, preventing recurrence of hyperkalaemia and reducing RAASi discontinuation.[14] A recent substudy of the OPAL-HK[18] conducted in older CKD patients taking RAASi, found that patiromer reduced recurrent hyperkalaemia and was well tolerated also in this subgroup.

Drug-drug interactions and adverse events

Because patiromer is not systemically absorbed, drug–drug interactions related to cytochrome P450 or systemic drug transporter effects are uncommon.[19] Patiromer showed no significant binding with many oral drugs, commonly used in patients with hyperkalaemia.[19] However, interactions with patiromer in the gastrointestinal tract may occur, reducing absorption of concomitant oral medications. For

Table 3 Main clinical trials on patiromer for the treatment of hyperkalaemia

Study (ref.)	Patients included	Primary endpoint(s)	Main results
PEARL-HF: Phase 2, prospective, randomized, double-blind, placebo-controlled, parallel-group clinical trial[15]	Patients with chronic HF and a history of hyperkalaemia or CKD	Change from baseline in serum K^+ at the end of treatment	Lower serum K^+ levels, lower incidence of hyperkalaemia
AMETHYST-DN: Phase 2, prospective, randomized, open-label, dose-ranging clinical trial[17]	Outpatients with hyperkalaemia, Type 2 diabetes mellitus, and CKD receiving an ACEi, ARB, or both ($n = 306$)	Decline in K^+ concentration from baseline to Week 4 or prior to dose-titration	Decreases in serum K^+ levels were observed at each monthly point, lasting through 52 weeks
OPAL-HK: Phase 3, two-phase, single-blind, randomized, placebo-controlled trial [16]	Initial phase: patients with Stage 3 or 4 CKD and hyperkalaemia stabilized on an RAASi ($n = 243$)	Initial phase: mean change in the serum potassium level from baseline to Week 4	Decrease in serum potassium levels and reduction in the recurrence of hyperkalaemia
	Randomized phase: patients who reached the target potassium level ($n = 107$)	Randomized phase: between group difference in the median change in the serum potassium level	

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CKD, chronic kidney disease; HF, heart failure; RAASi, renin-angiotensin-aldosterone system inhibitor.

this reason, it is advised to separate their administration by at least 3 h.[19] A study[20] showed that amlodipine, cinacalcet, clopidogrel, furosemide, lithium, metoprolol, trimethoprim, verapamil, and warfarin had no clinically significant interactions with patiromer and that ciprofloxacin, levothyroxine, and metformin had no clinically significant drug–drug interactions after separating their administration from that of patiromer by 3 h. Of note, two of these drugs (ciprofloxacin and levothyroxine) are known to interact with calcium. It is therefore recommended to separate concomitant medications containing calcium.[20]

Further studies are needed to evaluate drug–drug interactions of patiromer with quinidine and thiamine.

As for adverse events, the aforementioned clinical studies showed that patiromer was not associated with serious adverse events. Adverse events were similar among trials. The most commonly reported adverse events were gastrointestinal effects (i.e. constipation and diarrhoea) and electrolyte abnormalities (i.e. hypomagnesaemia) (*Table 2*), as also shown by a recent review and meta-analysis.[21] Taken all together, these data show patiromer to be well tolerated.[13]

Sodium zirconium cyclosilicate

Pharmacological properties and available data

A report by the EMA (25 January 2018-EMA/93250/2018-Committee for Medicinal Products for Human Use) stated that SZC is indicated for the treatment of hyperkalaemia in adult patients. Pharmacological properties of SZC have been described in detail elsewhere[22] and are summarized in *Table 2*. Briefly, this agent is an inorganic cation exchange crystalline compound that allows a thermodynamically favourable catching of potassium ions.[23] It acts within 1 h of administration by permanently removing excess potassium in the gastrointestinal tract.[22] Sodium zirconium cyclosilicate is mainly excreted in the faeces and not systemically absorbed.[23] The recommended initial dose is 10 g three times a day for up to 48 hours.

Clinical trials demonstrated a dose-dependent potassium-lowering effect of SZC (*Table 4*). In particular, the HARMONIZE trial[24] found that normokalaemia was achieved by 84% of patients within 24 h and by 98% of patients within 48 h. After 28 days, potassium level was significantly lower in all three SZC groups (i.e. 5 g, 10 g or 15 g) than placebo group and these reductions were dose-dependent.

Similar results were gained by a subgroup analysis[25] of this trial, conducted on 87 patients with heart failure, in whom serum potassium decreased to physiological levels within 48 h (*Table 4*).

A multicentre, two-stage, double-blind, and Phase 3 trial[26] found that SZC led to a dose-dependent reduction of potassium level within 48 h. A significant difference was found between the 2.5 g, 5 g, and 10 g groups when compared with placebo. Patients who reached normokalaemia (72%) were then randomized to receive either their original SZC dose or placebo. Results showed that patients receiving ZS-9.5 g and 10 g maintained normokalaemia during 3-14 days.

A Phase 2 randomized, double-blind, placebo-controlled, and dose-escalating clinical trial[27] in advanced CKD (*Table 4*) showed the efficacy of SZC in the 3 g and 10 g dosages.

Unfortunately, all these studies are limited by their short duration. An ongoing study is evaluating SZC safety and efficacy for up to 12 months with a 10 g standard dose to be adjusted in increments of 5 g.

Of note, SZC should not be used for the acute treatment of hyperkalaemia, as these patients were excluded from both trials.[22] On the other hand, it may be used as preventive treatment in patients with CKD or patients maintained on medications that affect potassium level.[22]

Table 4 Main clinical trials of sodium zirconium cyclosilicate for the treatment of hyperkalaemia

Study (Ref.)	Patients included	Primary endpoint(s)	Main results
Multicentre, two-stage, double-blind, randomized, placebo-controlled, dose-escalating, Phase 3 trial[26]	Initial phase: ambulatory outpatients with hyperkalaemia ($n = 754$) Maintenance phase: ambulatory outpatients with normal serum K^+ at 48 h ($n = 543$)	Initial phase: rate of change in mean serum K^+ concentration Maintenance phase: mean serum K^+ concentration compared with placebo	Decline in serum K^+ level at 48 h Normokalaemia maintained during maintenance phase (12 days)
HARMONIZE: multicentric, two-stage, double-blind, randomized, placebo-controlled, dose-escalating, Phase 3 trial[24]	Open-label phase: ambulatory outpatients with hyperkalaemia ($n = 258$) Randomized phase: ambulatory outpatients with normal serum K^+ at 48 h ($n = 237$)	Change in serum K^+ concentration Mean serum K^+ concentration in each SZC group compared with placebo	Serum K^+ level decreased to normal levels within 48 h All three doses of SZC resulted in lower serum K^+ levels and a higher proportion of patients with normal serum K^+ levels for up to 28 days
Substudy of the HARMONIZE[25]	HF patients with evidence of hyperkalaemia treated with open-label SZC for 48 h. Patients ($n = 87$; 60 receiving RAASi) who achieved normokalaemia	Rate of serum K^+ concentration decline in 28 days	All three SZC doses reduced serum K^+ and maintained normokalaemia for 28 days without adjusting concomitant RAASi therapy
Phase 2, prospective, randomized, double-blind, placebo-controlled, dose-escalating clinical trial[27]	Patients with stable Stage 3 CKD and mild-to-moderate hyperkalaemia ($n = 90$)	Rate of serum K^+ concentration decline in the first 48 h	Decline of serum K^+ in the 3 g and 10 g dosage groups

CKD, chronic kidney disease; HF, heart failure; RAASi, renin–angiotensin–aldosterone system inhibitor.

Drug–drug interactions and adverse events

Drug–drug interactions have not been fully investigated. Of note, this agent can transiently increase gastric pH and should be administered at least 2 h after or before other oral medications as suggested by the EMA. However, this separation is only needed if the concomitant drug displays pH-dependent solubility, i.e. highly soluble in acidic pH, leading to faster drug release.

Except for rare, controllable events such as urinary tract infections (1.1%) and oedema (0.9%), a recent meta-analysis[21] found that safety profile of SZC is similar to that of placebo.

Long-term clinical trials are needed to assess possible risks that may be related to SZC during chronic use.

Conclusions and suggestions for upcoming studies

Clinical studies of patiromer and SZC demonstrated a dose-dependent potassium-lowering effect for both these agents. They may be helpful in optimizing RAASi therapies in patients with hyperkalaemia. However, their benefits on long-term outcomes should be further evaluated in proper clinical trials. Although there are some concerns about hypomagnesaemia and positive calcium balance from patiromer, and sodium overload from SZC, both agents have been shown to be well tolerated.[9]

Upcoming clinical trials should aim to investigate whether these new treatments for hyperkalaemia could plausibly improve clinical outcomes in specific patient groups that are prone to arrhythmias (e.g. patients with pre-existing CV disease, or patients with advanced CKD).[28]

Despite these gaps of knowledge, in light of their pharmacological properties and available evidence collected so far, patiromer and SZC are promising agents in the management of hyperkalaemia in CV patients.

Conflict of interest: none declared.

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