Potassium-Binding Agents for the Clinical Management of Hyperkalemia

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INTRODUCTION

Potassium, the second most-abundant cation in the body, performs several important physiological functions, including cellular metabolism, glycogen and protein synthesis, and maintenance of the electrical action potential across cell membranes, especially in the myocardium.[1,2] Physiologic serum potassium levels range from 3.5 to 5.0 mEq/L. Hyperkalemia is defined as a serum potassium level exceeding 5 mEq/L; the disorder may be fatal when the potassium level is greater than 6.5 mEq/L.[3]

Hyperkalemia results from extracellular shifts of potassium, excessive ingestion of potassium, and/or impaired elimination of potassium by the kidneys.[3] It is a fairly common electrolyte disorder, affecting approximately 10% of hospitalized patients, and has the potential to cause life-threatening cardiac arrhythmias.[4] The clinical manifestations of hyperkalemia are associated with alterations in neuromuscular and cardiac function. Signs and symptoms of the disorder include muscle twitching, cramping, weakness, paralysis, paresthesia (face, hands, and feet), electrocardiogram (ECG) changes (e.g., peaked T-waves, a prolonged PR-interval, the loss of P waves, a widened QRS complex, and a shortened QT-interval), and arrhythmias (e.g., bradyarrhythmias, ventricular fibrillation, and asystole).[5,6]

Hyperkalemia is most commonly associated with renal insufficiency, heart failure, and the use of medications, including those that affect the renin–angiotensin–aldosterone system (RAAS), potassium-sparing diuretics, and nonsteroidal anti-inflammatory drugs (NSAIDs).[7] The diagnosis of hyperkalemia requires a complete clinical history, a review of the patient's medication profile, a physical examination, and the determination of serum potassium levels. In addition, a complete urine analysis should be performed and an ECG should be obtained.

The goals of treatment in patients with acute hyperkalemia are to reverse adverse cardiac effects, shift potassium into the cells, remove potassium from the body, ameliorate the patient's signs and symptoms, and normalize serum potassium levels while avoiding overcorrection. For patients who are chronically at risk for hyperkalemia, the main treatment goal is to control serum potassium levels.[8]

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In general, the treatment of hyperkalemia is governed by the patient's clinical presentation, by how rapidly the disorder developed, by the severity of the potassium abnormality, and by the presence of ECG changes.[1,8] Asymptomatic patients with mild hyperkalemia (defined as a serum potassium level of 5 to 6 mEq/L) usually do not require specific treatment.[1] For individuals with moderate (6 to 7 mEq/L) or severe (greater than 7 mEq/L) hyperkalemia, two general approaches can be used to lower serum potassium levels.[1] The first approach is to shift intracellular potassium using a combination of intravenous (IV) insulin plus glucose (to offset hypoglycemia), albuterol, or sodium bicarbonate.[9–11] This is only a temporary measure, however, and is best suited for the management of acute hyperkalemia. The second approach is to increase potassium elimination from the body. This may be accomplished through the use of cation exchange resins, loop diuretics, or dialysis. These interventions are essential to the management of severely increased potassium levels accompanied by life-threatening ECG changes.[12]

Although effective, dialysis is an expensive and intensive procedure that may not be practical for all hyperkalemic patients, particularly those with only slightly elevated serum potassium levels.[13,14] Loop diuretics, such as furosemide, are effective in these patients, but these agents are often associated with toxicities, making them impractical for certain patients as well.[15] In the setting of severe hyperkalemia and in the presence of ECG changes, it may be necessary to administer IV calcium to stabilize cardiac myocytes.[1]

Currently, the long-term treatment of hyperkalemia primarily involves the use of sodium polystyrene sulfonate (SPS) (SPS Suspension, Carolina Medical Products Company; Kayexalate [SPS powder], Sanofi-Aventis U.S.), a nonspecific sodium-cation exchange resin originally approved in 1958.[16–18] However, two potassium-binding agents, sodium zirconium cyclosilicate (ZS-9) and patiromer (Veltassa), appear to have the potential to challenge the dominance of SPS as hyperkalemia treatments (Table 1).

In this article, we preview the potential advantages and disadvantages of ZS-9 and patiromer, and compare these compounds with SPS.

SODIUM POLYSTYRENE SULFONATE

Although SPS has been around for nearly 60 years and is the mainstay of hyperkalemia therapy, its long-term efficacy in this setting has not been evaluated in randomized, placebo-controlled trials.[16–18] Moreover, the use of SPS is limited by its association with gastrointestinal (GI) adverse events (AEs) (e.g., constipation and diarrhea) as well as other systemic toxicities, including sodium loading, hypomagnesemia, hypocalcemia, and colonic necrosis.[19–21]

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Table 1 Potassium-Binding Agents for Treatment of Patients With Hyperkalemia

	Sodium Polystyrene Sulfonate	Sodium Zirconium Cyclosilicilate (ZS-9)	Patiromer (Valtessa)
FDA approval	1958	Pending	2015
Mechanism of action	Nonspecific sodium-cation exchange resin[20]	Selective potassium cation trapping agent[55]	Calcium-potassium cation exchange resin[45,48]
Formulation	• Oral suspension • Powder for reconstitution • Rectal enema[21,22]	• Oral suspension • Dissolvable tablet[35]	• Oral suspension[45]
Onset of action	1 to 2 hours[27]	1 hour[42]	7 hours[45,48]
Dosing	• 15–60 g/day orally (1–4 times daily) • 30–50 g/day rectally (up to 4 times daily)[21,22]	• 5–10 g once daily pending FDA approval[35]	• 8.4–25.2 g once daily[45]
Common adverse events	• GI disturbances (e.g., constipation, diarrhea, nausea, vomiting, gastric irritation) • Electrolyte disorders (e.g., hypokalemia, hypomagnesemia, hypocalcemia)[32] • Systemic alkalosis[21,22]	• GI disturbances (e.g., constipation, diarrhea, nausea, vomiting) • Hypokalemia[35–37]	• GI disturbances (e.g., constipation, diarrhea, nausea, vomiting, flatulence) • Hypokalemia[48,49] • Possible calcium load[39] • Hypomagnesemia[48,49,54]
Serious adverse events	Colonic necrosis[20,32]	None[35–37]	None[48,49,54]

In the past, SPS was often administered with sorbitol, a laxative, because of the potential for constipation and because of the ability of sorbitol to further increase potassium elimination. In 2009, however, the Food and Drug Administration (FDA) issued a warning with regard to the concomitant use of SPS and sorbitol after colonic necrosis and other serious GI AEs were reported.[22] Today, the use of SPS with sorbitol is not recommended.

Pharmacology

SPS is a cation-exchange resin administered orally or rectally (by enema).[21] Synthetic cation-exchange resins are insoluble polymers resembling a crystalline lattice. When placed in a solvent, this structure swells, allowing the exchange of ions between the reactive group on the resin (in the case of SPS, sodium) and ions dissolved in the solvent.[23] Although the goal of therapy with cation-exchange resins is to replace potassium ions, these resins are not exclusively selective for potassium; calcium and magnesium may bind to the structures as well.[21] As SPS moves through the intestine, sodium ions are released and exchanged for potassium ions. SPS, with its bound potassium, continues through the colon and is eventually eliminated in the feces.[21,22,24]

Pharmacokinetics and Pharmacodynamics

SPS is not absorbed into the systemic circulation and therefore has no systemic bioavailability. An *in vitro* study showed that each gram of resin binds to approximately 3.1 mEq of potassium.[25] However, the *in vivo* exchange capacity of SPS has been estimated at only approximately 33%, or 1 mEq of potassium per gram of resin,[21] and this number may be as low as 0.4 to 0.8 mEq per gram of resin.[26] This reduced exchange capacity is due to competition from other cations, particularly sodium, calcium, and magneisum.[27]

Dosing

In adults, SPS is administered as a suspension at a dosage of 15 g/60 mL given one to four times per day; a powdered formulation requiring reconstitution before administration is also available.[21] Alternatively, an enema containing 30 g/120 mL or 50 g/200 mL SPS may be administered every six hours in patients who are unable to take the oral preparations. The SPS enema should be retained as long as possible and followed by a sodium-free cleansing enema.[21]

The ability of SPS to lower serum potassium levels is dose-dependent (i.e., increasing doses are associated with increased reductions in serum potassium).[28] One study found that, 10 hours after administration, 15-g, 30-g, 45-g, and 60-g doses of SPS resulted in 0.82-mEq/L, 0.95-mEq/L, 1.11-mEq/L, and 1.4-mEq/L mean reductions in serum potassium levels, respectively ($P = 0.0003$).[28] In a retrospective review, the investigators determined that a 30-g dose of SPS resulted in an average reduction of 0.99 mEq/L in serum potassium levels. They concluded that a 30-g dose of SPS should be administered to patients with serum potassium levels of between 5 and 6 mEq/L, and that a 60-g dose should be given to those with serum potassium levels of greater than 6.0 mEq/L. The authors also recommended that clinicians wait 12 hours before administering additional doses of SPS.[29]

For small children and infants, SPS doses may be calculated based on 1 g of resin per mEq of targeted potassium. Alternative routes of administration may be necessary, such as enemas for neonates.[21]

Adverse Events and Clinical Monitoring

The AEs associated with SPS principally involve the GI system and include gastric irritation, nausea, vomiting, constipation, diarrhea, ischemic colitis, perforation, and bleeding.

Large doses of rectally administered SPS have resulted in fecal impaction in children and the elderly. Cases of intestinal necrosis, a potentially fatal complication, were also reported with the combination of SPS and sorbitol.[21,30] Acute bronchitis and bronchopneumonia have resulted from the inhalation of polystyrene sulfonate particles.[21]

Treatment with SPS has the potential to cause hypokalemia. Patients should be monitored for signs of this disorder, including prolongation of the QT interval, T-wave inversions, prominent U waves, cardiac arrhythmias, and severe muscle weakness leading to paralysis. In addition, serum potassium levels should be monitored regularly (at least one, two, four, six, and 24 hours after the initiation of treatment) in the acute-care setting.[31] Serum potassium levels may not reflect intracellular potassium stores; therefore, patients treated with SPS should be carefully monitored for rebound hyperkalemia.[31] Since SPS is not exclusively selective for potassium ions, patients should be monitored for other electrolyte disturbances, including hypomagnesemia and hypocalcemia. Caution is also advised in patients who cannot tolerate increased sodium loads, such as those with congestive heart failure, severe hypertension, or edema.[21]

Drug–Drug Interactions

As previously noted, the concomitant administration of SPS and sorbitol is no longer recommended because of the risk of intestinal necrosis. Systemic alkalosis has been reported after the oral administration of SPS in combination with nonabsorbable cation-donating antacids and laxatives; therefore, SPS should not be used with magnesium hydroxide. Moreover, concomitant administration of aluminum hydroxide may result in intestinal obstruction and should also be avoided. The hypokalemia associated with SPS may exacerbate the toxic effects of digitalis, and SPS may also reduce the absorption of lithium and thyroxine.[21,32]

Special Patient Populations

SPS is a pregnancy category C drug and should be used with caution in pregnant women. It is not known whether SPS is excreted in breast milk. The safety and efficacy of SPS in pediatric patients have not been established.[21]

Insulin and glucose are the preferred treatment options for hyperkalemia in preterm neonates, rather than rectally administered cation exchange resins.[33] If SPS is used in this cohort, it should be administered rectally with close monitoring. A major safety concern is the risk of fecal impaction, which can result in digestive-tract hemorrhage or colonic necrosis. SPS is contraindicated in patients with hypokalemia, a history of hypersensitivity to polystyrene sulfonate resins, or obstructive bowel disease.[21]

Clinical Efficacy

Although no randomized, controlled studies have evaluated SPS in hyperkalemic patients, other clinical data support its use in this setting. Key investigations include the following.

In the early 1960s, Scherr and colleagues evaluated the efficacy of SPS in 32 patients with acute or chronic renal disease and hyperkalemia. The patients received either 20 g to 60 g of oral SPS or 10 g to 40 g of SPS enema. After 24 hours, the mean reductions in serum potassium were 1.0 mEq for the oral dose and 0.8 mEq for the enema. Glucose and either insulin or sodium bicarbonate were administered concomitantly in some patients, and all of the patients had potassium-restricted diets.[17]

Flinn and colleagues administered SPS (5 g or 15 g) with 70% sorbitol four times per day in 10 oliguric patients. The use of sorbitol was intended to prevent constipation and to prolong retention of the resin. Serum potassium levels showed similar reductions with the combination treatment compared with sorbitol alone.[18]

Gruy-Kapral found that serum potassium levels were not reduced 12 hours after the administration of SPS (30 g), with or without a cathartic.[24] Emmett and colleagues, however, found that when SPS was combined with a cathartic, including sorbitol, more potassium was excreted than when sorbitol was used alone. Their findings indicated that the binding capacity of SPS is only 0.4 to 0.8 mEq per gram of resin

Kessler and colleagues conducted a retrospective cohort study to evaluate the responses to a single dose of oral SPS without a concomitant cathartic among 122 hyperkalemic patients. Ten hours after the administration of a single 15-g, 30-g, 45-g, or 60-g dose of SPS, the investigators observed mean serum potassium reductions of 0.82, 0.95, 1.11, and 1.40 mEq/L, respectively. After a single dose of SPS, the mean potassium concentration was within the normal range in 115 patients (94%).[27]

With regard to the long-term use of SPS, Chernin et al. conducted a nonrandomized retrospective study to evaluate the efficacy of low-dose, sorbitol-free SPS (15 g once daily) for the secondary prevention of hyperkalemia in 14 patients with chronic kidney disease (CKD) or heart disease, and with a history of RAAS inhibitor therapy. The subjects received SPS for a total of 289 months, with a mean follow-up period of 14.5 months. No further episodes of hyperkalemia were recorded while the patients were receiving SPS therapy, and none of the patients developed colonic necrosis or life-threatening events that could be attributed to the use of SPS.[34]

SODIUM ZIRCONIUM CYCLOSILICATE

Sodium zirconium cyclosilicate (ZS-9, ZS Pharma) is an inorganic sodium–potassium cation exchange agent currently undergoing clinical evaluation as a potential treatment for hyperkalemia. Two phase 3 trials have been completed, and a third is currently investigating long-term therapy.[35–38] In July 2015, the FDA accepted a new drug application for ZS-9 and set a Prescription Drug User Fee Act action date of May 26, 2016.[39]

Pharmacology

The trace element zirconium has several biomedical and chemical applications because of its low toxicity.[40] For example, zirconium silicates are employed in renal and hepatic dialysis to selectively extract ammonium ions.[41] Since ammonium and potassium cations have similar diameters, it was hypothesized that zirconium silicates could also be used clinically for the selective entrapment of potassium.[41]

ZS-9 is an orally administered, nonabsorbable, inorganic microporous compound composed of zirconium and silicate atoms with approximately 8% sodium by total weight. ZS-9 acts as a sodium–potassium cation exchanger, selectively trapping

potassium ions as it moves through the GI tract. The compound is believed to selectively filter potassium ions via the same mechanism used by physiologic potassium channels. The micropores on the structure of ZS-9 have diameters closely similar to those of potassium ions; as a result, ZS-9 does not capture sodium, calcium, or magnesium ions.[42]

Pharmacokinetics and Pharmacodynamics

ZS-9 is not systemically absorbed and is almost entirely eliminated in the feces.[35–38] *In vitro* studies simulating the physiological environment of the GI tract have shown that ZS-9 reaches potassium equilibrium in less than 20 minutes.[42] In *in vivo* studies, ZS-9 demonstrated potassium-lowering effects within one hour after the administration of a 10-g oral dose.[36,37] *In vivo*, ZS-9 has a 25-fold selectivity for potassium ions over calcium and magnesium ions. ZS-9 is expected to work throughout the GI tract. As the potassium concentration and pH increase along this route, the uptake of potassium by ZS-9 is rapid and sustained.[42]

Dosing

ZS-9 has demonstrated dose-dependent efficacy at reducing serum potassium levels when administered at doses of 0.3 g, 1.5 g, 2.5 g, 3 g, 5 g, 10 g, or 15 g in randomized, double-blind, placebo-controlled studies.[35,37] The compound was usually administered as a powder dissolved in 240 mL of water and administered with a full meal.[35–38] One phase 3 study reported the best results with doses of 5 g and 10 g.[37]

Adverse Events and Clinical Monitoring

No serious AEs were associated with the use of ZS-9 in clinical trials. GI disturbances (such as diarrhea and constipation) and edema were the most common AEs. The rates of GI events were similar between the ZS-9 and placebo groups.[36,37] Hypokalemia was another important AE. In one study, mild hypokalemia (3.0 to 3.4 mEq/L) resolved after dose adjustments.[36] In another study, patients treated with ZS-9 at 2.5 g and 10 g experienced one case each of hypokalemia (3.1 mEq/L and 3.4 mEq/L). Both cases resolved without potassium repletion.[37] ZS-9 has shown no dose-related effects on serum glucose levels, blood pressure, heart rate, or body weight.[35,36] However, the compound has not been evaluated for more than four weeks in clinical trials; therefore, its long-term safety and efficacy remain undetermined.[35–37]

Drug–Drug Interactions

To date, clinical studies have not identified significant drug–drug interactions involving ZS-9.[35–37]

Table 2 Pivotal Clinical Trials Evaluating Efficacy of Sodium Zirconium Cyclosilicilate (ZS-9) in Patients With Hyperkalemia

Trial Design	Primary Endpoint(s)	Results
Ash et al.[35]		
• Phase 2 randomized, double-blind, placebo-controlled, dose-escalation study in 90 patients with stable stage-3 CKD and hyperkalemia • *Treatment:* ZS-9 0.3 g (n = 12), 3 g (n = 24), 10 g (n = 24), or placebo (n = 30) for 2 days with meals	Rate of serum potassium decline in first 48 hours	• Primary endpoint met in 3 g ($P = 0.048$) and 10 g ($P < 0.0001$) cohorts vs. placebo • From baseline, mean serum potassium significantly reduced by 0.92 mEq/L at 38 hours
Kosiborod et al.[36] (HARMONIZE)		
• Phase 3, randomized, double-blind, placebo-controlled trial in outpatients with hyperkalemia • *Treatment:* ZS-9 (10 g) TID in 258 patients in initial 48-hour open-label phase; 237 patients with normokalemia at 48 hours received ZS-9 5 g (n = 45), 10 g (n = 51), 15 g (n = 56), or placebo (n = 85) QD for 28 days in randomized phase	Mean serum potassium level in each ZS-9 group vs. placebo during days 8–29 of randomized phase	• Serum potassium significantly lower on days 8–29 in all ZS-9 groups vs. placebo (4.8 mEq/L, 4.5 mEq/L, and 4.4 mEq/L for 5 g, 10 g, and 15 g, respectively, vs. 5.1 mEq/L for placebo; $P < 0.001$ for all comparisons) • Proportion of patients with mean potassium < 5.1 mEq/L on days 8–29 significantly higher in all ZS-9 groups compared with placebo (80%, 90%, and 94% for 5 g, 10 g, and 15 g vs. 46% for placebo; $P < 0.001$ for each dose vs. placebo)
Packham et al.[37]		
• Two-stage, phase 3, double-blind, placebo-controlled trial in patients with hyperkalemia • *Treatment:* ZS-9 1.25 g (n = 145), 2.5 g (n = 141), 5 g (n = 158), or 10 g (n = 143) or placebo (n = 158) TID for 48 hours in 753 patients (initial phase); 543 patients with normokalemia at 48 hours received ZS-9 or placebo QD on days 3–14 (maintenance phase)	Initial phase: exponential rate of change in mean serum potassium level at 48 hours; maintenance phase: between-group difference in mean serum potassium level during 12-day treatment interval	• Initial phase: mean exponential reduction from baseline per hour in serum potassium level at 48 hours: ZS-9 1.25 g, 0.11% ($P > 0.05$); 2.5 g, 0.16% ($P < 0.001$); 5 g, 0.21% ($P < 0.001$); and 10 g, 0.30% ($P < 0.001$) vs. placebo, 0.09% • Maintenance phase: ZS-9 5 g and 10 g significantly superior to placebo in maintaining normokalemia ($P = 0.008$ and $P < 0.001$, respectively)

CKD = chronic kidney disease; QD = once daily; TID = three times daily.

Clinical Efficacy

Table 2 summarizes the pivotal clinical studies of ZS-9 in hyperkalemia patients.[35–37] These studies are discussed below.

Ash et al.

Ash and colleagues conducted a phase 2, randomized, double-blind, placebo-controlled trial to assess the safety and efficacy of three doses of ZS-9 administered over a 48-hour period in 90 patients with stage-3 CKD (defined as an estimated glomerular filtration rate [eGFR] of 30 to 60 mL/min/1.73 m^2). The patients were randomly assigned to receive ZS-9 at doses of 0.3 g (n = 12), 3 g (n = 24), or 10 g (n = 24), or placebo (n = 30). Serum potassium levels (measured at hours 0.5, 1, 2, 4, 8, and 14 on day 1, and at hours 0, 4, 8, and 14 on day 2) were reduced in all four groups, with the greatest reduction occurring in the 10-g group. The latter patients experienced an average reduction of 0.92 mEq in serum potassium from baseline after 38 hours of treatment ($P < 0.001$). Serum potassium levels remained lower in the patients treated with ZS-9 than in those given placebo for up to 3.5 days after the last dose.[35]

Kosiborod et al. (HARMONIZE)

The phase 3, randomized, double-blind, placebo-controlled HARMONIZE (Hyperkalemia Randomized Intervention Multi-Dose ZS-9 Maintenance) trial evaluated the safety and efficacy of four weeks of treatment with ZS-9 in 258 ambulatory patients with hyperkalemia.[36] During an initial open-label phase, the patients received a 10-g dose of ZS-9 three times per day with meals for two days. This treatment demonstrated a 1.1-mEq/L decrease in serum potassium levels. The patients were then randomly assigned to receive three doses of ZS-9 (5 g [n = 45], 10 g [n = 51], or 15 g [n = 56]) or placebo (n = 85) once daily for 28 days. At the end of the randomized phase, serum potassium levels were significantly lower with all three doses of ZS-9 compared with placebo (4.8 mEq/L, 4.5 mEq/L, and 4.4 mEq/L for 5 g, 10 g, and 15 g, respectively, versus 5.1 mEq/L for placebo; $P < 0.001$ for all comparisons). Moreover, significantly more patients in the ZS-9 groups had mean serum potassium levels of less than 5.1 mEq/L compared with the placebo group (36/45 [80%], 45/50 [90%], and 51/54 [94%] for the 5-g, 10-g, and 15-g groups versus 38/82 [46%] for the placebo group; $P < 0.001$ for all comparisons).

Packham et al.

Packham and colleagues conducted a two-stage, phase 3, double-blind, randomized, placebo-controlled study to evaluate the effects of ZS-9 in 753 ambulatory patients with hyperkalemia.[37] The patients were initially assigned to receive ZS-9 1.25 g (n = 154), 2.5 g (n = 141), 5 g (n = 158), or 10 g (n = 143) or placebo (n = 158) three times daily for two days. At the end of this treatment phase, patients receiving 2.5 g, 5 g, and 10 g of ZS-9 experienced mean reductions of 0.46 mEq/L, 0.54 mEq/L, and 0.73 mEq/L in serum potassium levels, respectively, compared with a reduction of 0.25 mEq/L among those given placebo. The patients were then randomly assigned to receive either the same doses of ZS-9 as in the initial phase or placebo once daily before breakfast for 11 days. During the maintenance phase, the 5-g and 10-g doses were found to be superior to placebo in maintaining normal potassium levels ($P = 0.008$ and $P < 0.001$, respectively).

PATIROMER

Patiromer (Veltassa, Relypsa, Inc.) is an orally administered potassium-binding agent developed for the treatment of hyperkalemia. The FDA accepted a new drug application for the compound in December 2014,[43] and it was approved in October 2015.[44,45] In clinical trials, patiromer reduced hyperkalemia in patients with CKD, diabetes mellitus, hypertension, and heart failure, and in patients receiving RAAS inhibitors.[46]

Pharmacology

Patiromer is a high-capacity polymer that exchanges calcium for potassium as it moves through the GI tract. It consists of cross-linked fluoroacrylate units with a carboxylate group, which is responsible for the binding of potassium. Patiromer's primary site of action is the distal colon, where free potassium concentrations are highest. By binding to potassium in the GI tract, patiromer prevents its reabsorption into the systemic circulation and enhances its excretion in the feces.[47–50]

Pharmacokinetics and Pharmacodynamics

Patiromer is a tasteless, odorless powder that can be mixed with food or water for oral administration.[46,47] It is not metabolized as it moves through the GI tract and is not absorbed systemically.[47] Results from a phase 1 study demonstrated a statistically significant reduction in baseline serum potassium levels at seven hours after patiromer administration, and this reduction was maintained for 48 hours.[46] In the same study, patiromer demonstrated an *in vitro* binding capacity of 8.5 mEq to 8.8 mEq of potassium per gram of polymer at colonic pH. This resulted in a dose-dependent increase in fecal potassium excretion and a reduction in urinary potassium excretion.[46]

Dosing

A phase 3 trial demonstrated clinical efficacy, safety, and tolerability with patiromer doses as low as 12.8 g in patients with mild hyperkalemia and 21.4 g in those with moderate-to-severe hyperkalemia. The compound was administered with 40 mL of water at breakfast and dinner.[48] Two phase 1 studies indicated that patiromer could be tolerated at doses of up to 60 g per day.[51]

Current labeling calls for an initial starting dosage of 8.4 g once daily. The dose may be increased or decreased, as necessary, to reach the desired serum potassium concentration, up to a maximum dosage of 25.2 g once daily.[45]

Adverse Events and Clinical Monitoring

No serious AEs have been associated with the use of patiromer. In clinical trials, GI disturbances, such as constipation, diarrhea, nausea, vomiting, and flatulence, were the most common acute AEs.[48,49] Constipation and diarrhea were also the most common chronic AEs, occurring in 4.6% and 2.7% of patients, respectively.[52] Moreover, patiromer was associated with worsening of hypertension or CKD, hypoglycemia, hypokalemia (i.e., serum potassium levels of less than 3.5 mEq/L), and hypomagnesemia. After treatment with patiromer, patients should be monitored for the return of elevated serum potassium levels.[52]

Table 3 Pivotal Clinical Trials Evaluating Efficacy of Patiromer (Veltassa) in Patients With Hyperkalemia

Trial Design	Primary Endpoint	Results
Weir et al.[48] (OPAL-HK)		
• Single-group, single-blind initial treatment phase in 219 patients with CKD and hyperkalemia receiving RAAS inhibitors; 107 patients entered placebo-controlled, single-blind, randomized withdrawal phase • *Treatment:* patiromer 4.2 g or 8.4 g BID in patients with mild or moderate hyperkalemia, respectively, for 4 weeks (initial phase); patients continued with patiromer (n = 55) or switched to placebo (n = 52) for additional 8 weeks (withdrawal phase)	Between-group difference in median change in serum potassium level over first 4 weeks of withdrawal phase	Estimated median change in potassium level to week 4 of withdrawal phase: 0 mmol/L for patiromer vs. 0.72 mmol/L for placebo ($P < 0.001$)
Pitt et al.[49] (PEARL-HF)		
• Double-blind, randomized, placebo-controlled, parallel-group study in 105 patients with heart failure and history of hyperkalemia or CKD • *Treatment:* patiromer 15 g BID or placebo BID for 4 weeks	Mean change in serum potassium from baseline to end of study (day 28)	Significantly reduced mean serum potassium level with patiromer vs. placebo at end of treatment (between-group difference: –45 mEq/L [$P < 0.001$])
Bakris et al.[54] (AMETHYST-DN)		
• Phase 2, open-label, dose-ranging, randomized study in outpatients with type-2 diabetes and mild (n = 222) or moderate (n = 84) hyperkalemia • *Initial dosages:* for mild hyperkalemia, patiromer 4.2 g (n = 74), 8.4 g (n = 74), or 12.6 g (n = 74) BID; for moderate hyperkalemia, patiromer 8.4 g (n = 26), 12.6 g (n = 28), or 16.8 g (n = 30) BID; all patients received RAAS inhibitors	Mean change in serum potassium level from baseline to week 4 or before initiation of dose titration	Mean reductions in serum potassium levels in patients with mild hyperkalemia: 4.2 g, 0.35 mEq/L; 8.4 g, 0.51 mEq/L; 12.6 g, 0.55 mEq/L Mean reductions in serum potassium levels in patients with moderate hyperkalemia: 8.4 g, 0.87 mEq/L; 12.6 g, 0.97 mEq/L; 16.8 g, 0.92 mEq/L

BID = twice daily; CKD = chronic kidney disease; RAAS = renin–angiotensin–aldosterone system.

Drug–Drug Interactions

Patiromer's prescribing information includes a boxed warning advising the administration of other oral medications at least six hours before or six hours after administration of patiromer.[45] *In vitro*, 28 drugs were tested and half of them showed greater than 30% binding with patiromer. Greater than 50% binding was demonstrated with amlodipine, cinacalcet, ciprofloxacin, levothyroxine, quinidine, thiamine, and trimethoprim, while 30% to 50% binding was demonstrated with clopidogrel, furosemide, lithium, metformin, metoprolol, verapamil, and warfarin. Due to concerns of drug interactions with untested, concomitantly administered medications, the FDA determined that six hours was a sufficient time period for separation of administration.[53]

Clinical Efficacy

Tables 3 summarizes the pivotal clinical studies of patiromer in patients with hyperkalemia.[48,49,54] These studies are discussed below.

Weir et al. (OPAL-HK)

A two-part, single-blind, phase 3 study (the OPAL-HK trial) was conducted to evaluate the safety and efficacy of patiromer in 237 patients with stage-3 or stage-4 CKD (i.e., eGFR of 15 to less than 60 mL/min/1.73 m^2) and hyperkalemia who were receiving RAAS inhibitors.[48] In this study's initial phase, the patients were randomly assigned to receive either 4.2 g or 8.4 g of patiromer twice daily, depending on the severity of their hyperkalemia. Dosage adjustments were allowed. After four weeks, 107 patients whose potassium levels were in the target range were randomly assigned to continue treatment with patiromer or to receive placebo for another eight weeks.

After the initial four weeks of patiromer treatment, the mean reduction from baseline in serum potassium levels was 1.01 mEq/L ($P < 0.001$). Serum potassium levels within the target range were achieved by 76% of the patients during this phase. Four weeks after rerandomization to patiromer (n = 55) or placebo (n = 52), the median changes in serum potassium levels were 0.72 mEq/L for placebo and 0 mEq/L for patiromer. A recurrence of hyperkalemia occurred in 15% of the patiromer group compared with 60% of placebo group through week 8 ($P < 0.001$).[48]

Pitt et al. (PEARL-HF)

The phase 2b, randomized, placebo-controlled, double-blind PEARL-HF (Multicenter, Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose to Evaluate the Effects of RLY5016 in Heart Failure Patients) trial was conducted to evaluate the safety and efficacy of patiromer in 104 heart failure patients receiving standard therapy and spironolactone.[49] The patients were randomly assigned to treatment with either patiromer (15 g) twice daily (n = 55) or placebo twice daily (n = 49) for four weeks. The patients treated with patiromer demonstrated a mean reduction in serum potassium levels of 0.45 mEq/L ($P < 0.001$) compared with the placebo-treated patients.

Bakris et al. (AMETHYST-DN)

The phase 2, open-label, randomized, dose-ranging AMETHYST-DN (Treatment of Hyperkalemia in Patients With Hypertension and Diabetic Nephropathy) trial was designed to evaluate the long-term safety and efficacy of patiromer in 306 outpatients with hyperkalemia, hypertension, and type-2 diabetes (eGFR: 15 to less than 60 mL/min/1.73 m^2 and serum potassium level greater than 5.0 mEq/L).[54] The patients were randomly assigned to receive 4.2 g (n = 74), 8.4 g (n = 74), or 12.6 g (n = 74) of patiromer twice daily for mild hyperkalemia (defined as a serum potassium level of 5.0 to 5.5 mEq/L), or 8.4 g (n = 26), 12.6 g (n = 28), or 16.8 g (n = 30) of patiromer twice daily for moderate hyperkalemia (defined as a serum potassium level of 5.5 to 5.9 mEq/L). All of the patients received RAAS inhibitors during the study.

The primary efficacy endpoint was the mean change in the serum potassium level from baseline to week 4 or before the initiation of dose titration. The mean reductions in serum potassium from baseline to week 4 for patients with mild hyperkalemia were 0.35 mEq/L, 0.51 mEq/L, and 0.55 mEq/L in the patients receiving 4.2 g, 8.4 g, and 12.6 g of patiromer, respectively. In patients with moderate hyperkalemia, the corresponding mean reductions in serum potassium were 0.87 mEq/L, 0.97 mEq/L, and 0.92 mEq/L. From week 4 through week 52, statistically significant mean decreases in serum potassium levels were observed at each monthly time-point in patients with mild or moderate hyperkalemia.[54]

DIFFERENCES AMONG THE POTASSIUM-BINDING AGENTS IN THE TREATMENT OF HYPERKALEMIA

Cation Selectivity

Both ZS-9 and patiromer appear to offer advantages over the current standard of care, SPS, for patients with hyperkalemia. All three of these agents work by binding potassium in the GI tract, but ZS-9 and patiromer have shown greater selectivity for potassium over other monovalent and divalent cations in clinical trials. SPS has limited selectivity for potassium and can bind and eliminate other cations, including calcium and magnesium, potentially resulting in clinically relevant electrolyte disturbances.[49] Patiromer offers another advantage by exchanging calcium ions, rather than sodium, for potassium. This is a desirable characteristic for patients who are sensitive to exogenous sodium delivery, including those with heart failure or cirrhosis.[46] Theoretically, the exchange of potassium for calcium increases the risk of hypercalcemia due to calcium load. To date, none of the trials evaluating patiromer has reported the occurrence of hypercalcemia.[48]

Onset of Action

ZS-9 has demonstrated the fastest onset of action in *in vivo* studies (within one hour at a dose of 10 mg).[36,37] The onset of action for SPS is one to two hours.[27] Patiromer provided statistically significant reductions in baseline serum potassium levels within seven hours after dosing, and this reduction was maintained for 48 hours.[46]

Administration and Safety

In clinical trials, patiromer was administered twice daily for maintenance therapy, whereas ZS-9 was administered once daily. The once-daily dosing of ZS-9 has the potential to improve patient adherence. However, for the initial lowering of potassium over 48 hours, ZS-9 was typically administered three times daily.[36,37,48] SPS may be administered via oral suspension one to four times daily, depending on the desired total dose.[21,22] All three agents are available as oral suspensions. In addition, SPS can be used as an enema, and ZS-9 is supplied as a tablet.

SPS, ZS-9, and patiromer are similar in terms of their adverse effects. The three agents most commonly cause GI disturbances, such as diarrhea and constipation, and all three require close monitoring for hypokalemia. The FDA issued a warning regarding the potential for intestinal necrosis with the use of SPS, but it was demonstrated that this AE resulted primarily from concomitantly administered sorbitol.[22,30]

CONCLUSION

Hyperkalemia is a potentially life-threatening electrolyte disorder.[4–6] Currently, the predominant treatment for chronic hyperkalemia is SPS, a nonspecific sodium–cation exchange resin.[20–22] The use of SPS, however, is limited by its GI adverse effects, such as diarrhea and constipation, and other systemic toxicities, including hypomagnesemia, hypocalcemia, and colonic necrosis.[19–21]

Sodium zirconium cyclosilicate (ZS-9, ZS Pharma) and patiromer (Veltassa, Relypsa, Inc.) are expected to offer greater binding selectivity for potassium compared with that of SPS.[48,55] Like SPS, however, both agents have been associated with GI disturbances and hypokalemia in clinical trials.[35–37,48,49]

SPS is available as an oral suspension, a powder for reconstitution, and an enema preparation. ZS-9 and patiromer were also developed as oral suspensions. In addition, ZS-9 will be marketed as a more-convenient dissolvable tablet, if approved by the FDA.[21,35,47]

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