



Potassium Binders Therapeutic Class Review (TCR)

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MANAGEMENTSM

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
patiomer (Veltassa®) ¹	Relypsa/Vifor	Treatment of hyperkalemia
sodium polystyrene sulfonate (SPS) ²	generic	<i>Limitation of use:</i> should not be used as an emergency treatment for life-threatening hyperkalemia because of delayed onset of action
sodium zirconium cyclosilicate ³ (Lokelma™)	AstraZeneca	

OVERVIEW

In the body, potassium (K) is stored primarily intracellularly, while sodium (Na) is the major extracellular cation.^{4,5} Together, this difference in distribution, maintained by the Na-K-ATPase pump in the cell membrane, provides the resting membrane potential that is the ultimate basis for cellular function. Changes to serum potassium levels, high or low, affect this membrane potential and can lead to impaired cellular function. In most patients, potassium homeostasis is maintained via a balance of potassium intake, distribution in the body, and secretion by the kidneys. Even as potassium intake increases in most healthy individuals, the body regulates excretion to maintain appropriate serum potassium levels. Conditions or medications affecting the ability of the kidneys to regulate potassium or changes in the ability of the Na-K-ATPase pump, directly or indirectly via the endocrine system (e.g., aldosterone, insulin), can cause impaired potassium adaptation. In addition, pseudohyperkalemia can result from increased potassium release from cells as a result of trauma, tissue breakdown, or acidosis, among other conditions.

Hyperkalemia is typically defined as serum potassium exceeding 5.5 mEq/L in adults, although sometimes a lower threshold of 5 mEq/L is used. Manifestations of hyperkalemia include muscle weakness or paralysis, neurologic impairment, cardiac conduction abnormalities, and bradyarrhythmias.^{6,7,8} These occur most commonly at chronically high potassium levels (e.g., ≥ 7 mEq/L) or in those with acute elevations above normal potassium levels. Hyperkalemia can also decrease urinary acid secretion, potentially leading to metabolic acidosis as well. Some of the most common conditions and medications resulting in hyperkalemia include acute or chronic renal impairment (impaired excretion), uncontrolled hyperglycemia (extracellular potassium shift), diabetes, heart failure, and medications affecting the renin-angiotensin-aldosterone system (RAAS) (e.g., angiotensin-converting enzyme inhibitors [ACE-I], angiotensin receptor blockers [ARBs]).

In an acute situation, hyperkalemia is often treated by shifting potassium intracellularly. In the meantime, treatment to increase potassium excretion may also administered, if safe to do so. Potassium binders, dialysis, and loop diuretics can all increase potassium excretion.^{9,10} Notably, potassium binders are not approved for the treatment of emergency hyperkalemia. Chronic hyperkalemia is often mild or moderate in severity and typically can be managed more slowly by addressing the underlying disorder, adjusting dietary potassium intake or causative medications, and/or use of loop diuretics or potassium binders. For several years, the only potassium binder available was sodium polystyrene sulfonate (SPS), once marketed under the trade name Kayexalate®; however, patiomer (Veltassa) and sodium zirconium cyclosilicate (Lokelma) received FDA approval for hyperkalemia in 2015 and 2018, respectively.¹¹ Recommendations from professional organizations guiding treatment with potassium binders are lacking.^{12,13,14,15} Generally, in patients with chronic hyperkalemia despite diuretics and correction of metabolic acidosis, patiomer and sodium zirconium cyclosilicate can be considered and titrated based on serum potassium levels. Furthermore, use of either of these potassium binders may permit patients

to continue RAAS therapy.¹⁶ Although SPS is commonly used, it has been associated with intestinal necrosis, perforation, and a two-fold increased risk for serious GI toxicity; therefore, some experts recommend not to use SPS in chronic mild or moderate hyperkalemia patients who are not experiencing a hyperkalemic emergency and not requiring rapid decreases in potassium levels.¹⁷

PHARMACOLOGY^{18,19,20}

Patiomer (Veltassa) is a cation exchange polymer that contains a calcium-sorbitol counterion as patiomer sorbitex calcium; it increases fecal potassium excretion via potassium binding in the lumen of the gastrointestinal (GI) tract, reducing free potassium. Ultimately, this leads to a reduction of serum potassium levels; it is not absorbed. Each gram of patiomer is equivalent to approximately 2 grams of patiomer sorbitex calcium.

Like patiomer, sodium polystyrene sulfonate is a non-absorbed, cation exchange polymer that contains a counterion (sodium) and reduces free potassium via potassium binding in the lumen of the GI tract. With the resin in the intestine (oral administration) or retained in the colon, the sodium ions are partially released and replaced by potassium ions (primarily in the large intestine). The approximate exchange ratio is 1 mEq potassium per 1 gram of resin, although this is unpredictably variable.

Sodium zirconium cyclosilicate (Lokelma) preferentially captures potassium in exchange for hydrogen and sodium. Like patiomer, it increases fecal potassium excretion via potassium binding in the lumen of the GI tract, reducing free potassium. It also is not absorbed and has a high affinity for potassium versus other cations (e.g., calcium, magnesium) *in vitro*.

PHARMACOKINETICS^{21,22,23}

Patiomer (Veltassa), sodium polystyrene sulfonate, and sodium zirconium cyclosilicate (Lokelma) are not systemically absorbed; however, the *in vivo* efficiency of sodium polystyrene sulfonate is approximately 33% (approximately 33% of the sodium content is delivered to the body).

The onset of action of oral sodium polystyrene sulfonate is usually ≥ 2 hours and peaks at 4 to 6 hours.²⁴ The duration of action of sodium polystyrene sulfonate is ≥ 4 to 6 hours.²⁵ The effect of the other agents in this class is delayed as well, due to their mechanism of action described above; the onset of patiomer is approximately 7 hours with a duration of approximately 48 hours. Consequently, these agents are not appropriate for the emergency treatment of hyperkalemia.

CONTRAINDICATIONS/WARNINGS^{26,27,28}

Contraindications

Patiomer (Veltassa) is contraindicated in patients with known serious hypersensitivity to the drug or any of its components. Mild to moderate hypersensitivity reactions, including edema of the lips, were reported in clinical trials.

Sodium polystyrene sulfonate is contraindicated in patients with known hypersensitivity to resins, obstructive bowel disease, and in neonates with reduced gut motility.

There are no contraindications associated with sodium zirconium cyclosilicate.

Warnings

Patiromer and sodium zirconium cyclosilicate carry a warning for worsening of GI motility. As a result, patiromer should be avoided in patients with severe constipation, abnormal post-operative motility disorders, and bowel obstruction/impaction.

Patiromer has a warning regarding hypomagnesemia. Serum magnesium should be monitored and supplemented, if needed, as patiromer can bind magnesium in the colon.

Sodium polystyrene sulfonate carries a warning for intestinal necrosis; cases of intestinal necrosis and other severe, and sometimes fatal, GI adverse events (e.g., perforation, ischemic colitis) have been reported. The majority of these cases involved concomitant use of sorbitol, which is not recommended, and occurred in patients with other risk factors for GI adverse events. It should only be used in patients who have normal bowel function and should be avoided in patients who have not had a bowel movement post-surgery. It should also be discontinued in patients who develop constipation.

Sodium polystyrene sulfonate also has warnings for electrolyte disturbances and fluid overload in select patients. Hypokalemia can occur, and since sodium polystyrene sulfonate is not selective for only potassium, magnesium and calcium may also be decreased; magnesium and calcium should also be monitored. Each 15 gram dose of sodium polystyrene sulfonate contains 1,500 mg (60 mEq) of sodium; therefore, patients sensitive to sodium intake should be monitored for signs of edema.

Cases of acute bronchitis or bronchopneumonia caused by inhalation of sodium polystyrene sulfonate particles have been reported; it should be administered to patients in an upright position and select patients (e.g., impaired gag reflex, altered level of consciousness, those prone to regurgitation) may be at an increased risk.

Sodium polystyrene sulfonate carries a warning for drug interactions as it may bind to select other medications and alter their effect.

Sodium zirconium cyclosilicate contains approximately 400 mg of sodium in each 5 gram dose; however, the extent of absorption is not known. Nonetheless, patients should be monitored for signs of edema. Patients who restrict their sodium intake or who are prone to fluid overload should be closely monitored and advised to adjust dietary sodium or increase their dose of diuretics, if necessary. In clinical trials of patients who were not on dialysis, edema was seen most commonly in patients treated with 15 grams once daily and was typically mild to moderate in nature. In a clinical trial of patients on chronic hemodialysis (most patients treated with 5 to 10 grams once daily on non-dialysis days), no difference in the average change from baseline in interdialytic weight gain was seen between the sodium zirconium cyclosilicate- and placebo-treated patients. Hemodialysis patients may be more susceptible to acute illness resulting in an increased risk for hypokalemia (e.g., illnesses leading to reduced oral intake, diarrhea); thus, consideration should be made for dose adjustments based on potassium levels in these patients.

Due to its radio-opaque properties, sodium zirconium cyclosilicate may give the appearance typical of an imaging agent; clinicians should be aware of this during abdominal X-ray procedures.

DRUG INTERACTIONS^{29,30,31}

Clinical studies have demonstrated decreased systemic exposure of some coadministered oral medications (e.g., ciprofloxacin, levothyroxine, metformin) with patiomer (Veltassa). Administration of other oral medications should be separated from patiomer by at least 3 hours.

As described above, sodium polystyrene sulfonate may bind to orally administered medications; administer other oral medications ≥ 3 hours before or ≥ 3 hours after sodium polystyrene sulfonate (patients with gastroparesis may require a 6 hour separation).

Sodium zirconium cyclosilicate (Lokelma) can lead to transient increases in gastric pH and may affect the absorption of co-administered drugs that exhibit pH-dependent solubility if taken close to the time sodium zirconium cyclosilicate is administered. During *in vivo* testing in healthy volunteers, an increase in systemic exposure to weak acids (e.g., furosemide, atorvastatin) and a decrease in systemic exposure to weak bases (e.g., dabigatran) were found when coadministered with sodium zirconium cyclosilicate. Other oral medications should be administered at least 2 hours prior or 2 hours after sodium zirconium cyclosilicate.

ADVERSE EFFECTS^{32,33,34}

Drug	Abdominal Discomfort	Constipation	Diarrhea	Edema	Flatulence	Hypersensitivity Reactions	Hypokalemia	Hypomagnesemia	Nausea
patiromer (Veltassa) (n=666)	2	7.2	4.8	nr	2	0.3	4.7	5.3	nr
sodium polystyrene sulfonate*	nr	reported	reported	nr	nr	nr	nr	nr	reported
sodium zirconium cyclosilicate (Lokelma) (n=1,009)	nr	nr	nr	4.4 to 16.1 (2.4)	nr	nr	4.1	nr	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and are not meant to be comparative or all inclusive. Incidences for the placebo group, when available, are indicated in parentheses. nr = not reported.

* Data based on postmarketing reports.

The following postmarketing adverse reactions have also been reported with sodium polystyrene sulfonate: anorexia, fecal impaction, gastric irritation, gastrointestinal concretions (bezoars), intestinal obstruction (due to concentration of aluminum hydroxide), ischemic colitis, systemic alkalosis, ulcerations, and vomiting.

In a clinical trial in patients on chronic hemodialysis assessing of sodium zirconium cyclosilicate, 5% of patients in both the sodium zirconium cyclosilicate and placebo groups experienced pre-dialysis hypokalemia (serum potassium < 3.5 mEq/L), and 3% of the sodium zirconium cyclosilicate-treated patients compared to 1% of placebo-treated patients experienced a serum potassium < 3 mEq/L.

SPECIAL POPULATIONS^{35,36,37}

Pediatrics

Safety and effectiveness of patiomer (Veltassa), sodium polystyrene sulfonate, or sodium zirconium cyclosilicate (Lokelma) in patients < 18 years old have not been studied.

The resin exchange rate is expected to be approximately the same in pediatrics as it is in adults (1 mEq potassium per 1 gram of resin); however, oral sodium polystyrene sulfonate should not be given to neonates. While not FDA-approved in this population, excessive doses or inadequate dilution of sodium polystyrene sulfonate can result in resin impaction in children and neonates, and premature or low birth weight infants may be at a greater risk for GI adverse effects.

Geriatrics

No differences were seen in clinical trials of patiomer (Veltassa) in patients ≥ 65 years old compared to younger adults; however, this population reported more GI adverse reactions compared to younger patients.

No differences were seen in clinical trials of sodium zirconium cyclosilicate (Lokelma) in patients ≥ 65 years old compared to younger adults.

Pregnancy

Use of these agents is not anticipated to cause fetal risk as they are not systemically absorbed.

Renal Impairment

No dosage adjustment of patiomer (Veltassa) is required in patients with renal impairment.

DOSAGES^{38,39,40}

Drug	Starting Dose	Titration	Administration	Available Strengths
patiomer (Veltassa)	8.4 grams orally once daily	Adjusted based on target potassium range and serum potassium; Doses should be titrated up in ≥ 1 week intervals in 8.4 gram intervals to a maximum dose of 25.2 grams once daily if needed	Prepare immediately prior to administration; Measure 1/3 cup of water and pour half of this (approximately 1/6 cup) into a glass, add patiomer, and stir, then add the remaining water and stir thoroughly; Drink, adding water for desired consistency or if needed, until all powder is dissolved and ingested; Other beverages or soft foods (e.g., apple sauce, yogurt) may be used instead of water to prepare the mixture by following the same steps; the potassium content of these liquids or soft food should be considered as part of the dietary recommendations on potassium intake for the patient; Administer with or without food, but separate from other oral medication administration by at least 3 hours; Do not take dry, heated, or add to heated foods or liquids; Store in the refrigerator; if stored at room it must be used within 3 months; avoid excessive heat	8.4 gram, 16.8 gram, and 25.2 gram single-use powder packets in packages of 1, 4, or 30 packets (contains xanthan gum)
sodium polystyrene sulfonate	Dosage depends on severity and resistance of hyperkalemia	Oral: average total daily adult dose = 15 grams to 60 grams, administered as a 15-gram dose (4 level teaspoons), 1 to 4 times daily Rectal: average adult dose = 30 grams to 50 grams every 6 hours	Prepare and use within 24 hours; do not heat Oral: suspend each dose in a small amount of water or syrup, approximately 3 to 4 mL of liquid per gram of resin; Administer with patient in an upright position; Separate from other oral medication administration by at least 3 hours (patients with gastroparesis may require a 6-hour separation) Rectal: following an initial cleansing enema, insert a soft, large size (French 28) rubber tube into the rectum approximately 20 cm in (with the tip well into the sigmoid colon) and tape in place; Administer as a warm (room temperature emulsion in 100 mL of aqueous vehicle and flush with 50 to 100 mL of fluid (a thicker suspension may be used, but should not form a paste); Agitate the emulsion gently during administration; Retain for as long as possible and follow by a cleansing enema (adequate volume, up to 2 L) with a non-sodium-containing solution	Powder for suspension in 15 gram bottles and 454 gram jars (each level teaspoon contains approximately 3.5 g sodium polystyrene)

Dosages (continued)

Drug	Starting Dose	Titration	Administration	Available Strengths
sodium zirconium cyclosilicate (Lokelma)	<p>10 grams orally administered 3 times a day for up to 48 hours</p> <p>Chronic hemodialysis: 5 grams once daily on non-dialysis days; 10 grams once daily on non-dialysis days can be considered when potassium > 6.5 mEq/L</p>	<p>10 grams once daily, with a recommended maintenance dose range of 5 grams every other day to 15 grams daily; Dose should be adjusted as needed based on serum potassium level and desired target range and may be titrated at ≥ 1 week intervals in 5 gram increments</p> <p>Chronic hemodialysis: recommended maintenance dose range of 5 grams to 15 grams once daily on non-dialysis days; dose should be adjusted as needed based on serum potassium level and desired target range based on the pre-dialysis serum potassium after the long interdialytic interval; evaluate serum potassium after 1 week during initiation and following a dose adjustment; discontinue or decrease the dose if potassium falls below the desired target range based on the pre-dialysis value after the long interdialytic interval or clinically significant hypokalemia develops</p>	<p>Empty contents of packet into a glass containing at least 3 tablespoons of water, stir well and drink immediately; If powder remains in the glass, add water, stir and drink immediately until the entire dose is taken; Separate from other oral medication administration by at least 2 hours</p>	<p>5 gram and 10 gram powder packets in packages of 1, 11, or 30 packets</p>

CLINICAL TRIALS

Search Strategies

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials for FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance. Due to a paucity of data, single-blind and open-label trials that were considered for FDA approval have been included.

patiomer (Veltassa)

OPAL-HK: The safety and efficacy of patiomer were evaluated in a two-part, single-blind, phase 3 trial in patients with chronic kidney disease (CKD) taking RAAS inhibitors with a baseline serum potassium of 5.1 to 6.5 mEq/L (n=243).⁴¹ The first part consisted of a 4-week, single-group, single-blind initial treatment phase of 237 patients assigned to patiomer based on hyperkalemia severity (5.1 to < 5.5 mEq/L [mild] = 4.2 g twice daily or 5.5 to < 6.5 mEq/L [moderate to severe] = 8.4 g twice daily). At week 4, the mean change in serum potassium from baseline was -1.01 mEq/L (95% confidence interval [CI], -1.07 to -0.95; p<0.001), and 76% (95% CI, 70 to 81) of the 109 patients eligible for evaluation had reached the goal potassium level (3.8 to < 5.1 mEq/L). The change in patients with mild hyperkalemia was approximately half that for patients with moderate hyperkalemia (mild: -0.65 mEq/L [95% CI, -0.74 to -0.55]; moderate to severe: -1.23 [95% CI, -1.31 to -1.16]), and the mean dose of patiomer was 12.8 g/day and 21.4 g/day in the mild and moderate to severe groups, respectively. The second part of the trial consisted of an 8-week, placebo-controlled, single-blind, randomized withdrawal phase in 107 patients from the first part with a decreased potassium of 3.8 to < 5.1 mEq/L (from 5.5 to < 6.5 mEq/L). Patients were assigned to continue patiomer or to placebo. At week 8, the mean change in serum potassium from randomization was 0.72 mEq/L in the placebo group and 0 mEq/L in the patiomer group (difference, 0.72 mEq/L; 95% CI, 0.46 to 0.99; p<0.001). A potassium level of 5.5 mEq/L or greater occurred in 60% and 15% of patients in the placebo and patiomer groups, respectively, through week 8 (p<0.001). Analysis of the various subgroups, including presence of diabetes, gender, age, presence of heart failure, also favored patiomer over placebo. The most commonly reported adverse effect was constipation (11%) and hypokalemia occurred in 3%. A prespecified subanalysis of the OPAL-HK trial demonstrated statistically significant reductions in serum aldosterone, blood pressure, and albumin-to-creatinine ratio as the potassium decreased.⁴² No statistically different change in plasma renin was noted. During the withdrawal phase, aldosterone levels were sustained in the treatment group (versus increased with placebo), and blood pressure was significantly reduced in the treatment group (versus no

change with placebo). The authors concluded that patiromer reduces serum potassium and aldosterone levels independent of plasma renin activity in CKD patients using RAAS inhibitors.

sodium polystyrene sulfonate

Limited data are published evaluating the efficacy and safety of sodium polystyrene sulfonate for the treatment of hyperkalemia, although it has been available for several years.⁴³ Often these studies also have included comparator or coadministered agents that are no longer available or recommended (e.g., sorbitol), are not approved in the US, predate modern treatment options (e.g., chronic hemodialysis), and/or were completed in limited populations.^{44,45,46,47} Along with the lack of published data demonstrating efficacy, its use has also been associated with serious adverse effects.⁴⁸

sodium zirconium cyclosilicate (Lokelma)

In a multicenter, 2-stage, double-blind, phase 3 trial, 753 patients were randomized to receive 1 of 4 doses of sodium zirconium cyclosilicate (1.25 g, 2.5 g, 5 g, or 10 g) or placebo 3 times daily for the initial 2 days of the acute phase.⁴⁹ The primary endpoint in the acute phase was the difference in the exponential rate of change in serum potassium levels when comparing placebo-treated patients to those receiving sodium zirconium cyclosilicate. A greater reduction in the serum potassium level was seen in the 2.5 g, 5 g, and 10 g dose groups compared to placebo ($p < 0.001$ for all versus placebo). The reductions in serum potassium for the 2.5 g, 5 g, and 10 g dose groups were dose-dependent, and patients with higher starting potassium levels had a greater response to sodium zirconium cyclosilicate. Patients receiving 10 g three times daily had a mean reduction in serum potassium of -0.7 mEq/L. Patients who achieved a potassium level between 3.5 mEq/L and 4.9 mEq/L after the acute phase were then randomized to receive 1.25 g, 2.5 g, 5 g, or 10 g of sodium zirconium cyclosilicate or placebo once daily for 12 days for the maintenance phase of the trial. The study met the primary efficacy endpoint for the maintenance phase, the difference in the exponential rate of change in serum potassium levels over the 12-day treatment interval, at the 5 g and 10 g doses when compared to placebo ($p < 0.01$ and $p < 0.001$, respectively). Adverse events were similar in the treatment and placebo groups, with diarrhea being reported most commonly in both groups.

HARMONIZE: A 4-week, phase 3, multicenter, randomized, double-blind, placebo-controlled trial evaluated the safety and efficacy of sodium zirconium cyclosilicate in 258 patients with hyperkalemia (serum potassium ≥ 5.1 mEq/L).⁵⁰ During the initial 48-hour, open-label phase, patients received 10 g of zirconium cyclosilicate 3 times daily. Those who achieved normokalemia (3.5 mEq/L to 5 mEq/L) during the initial phase were then randomized to receive 1 of 3 doses of sodium zirconium cyclosilicate (5 g, 10 g, or 15 g) or placebo daily for a 28-day withdrawal phase. The primary endpoint in the withdrawal phase was the mean serum potassium value over the period from Day 8 to Day 29. In the initial phase, the median time to normalization was 2.2 hours, and 84% (95% CI, 79 to 88) and 98% (95% CI, 96 to 99) of patients had normokalemia by 24 and 48 hours, respectively. During the withdrawal phase, all 3 doses maintained mean potassium at lower levels than placebo (mean serum potassium of 4.8 mEq/L, 4.5 mEq/L, and 4.4 mEq/L in the 5 g, 10 g, and 15 g dose groups, respectively, versus 5.1 mEq/L in the placebo group; $p \leq 0.001$ for all treatment doses versus placebo). A greater proportion of patients had mean serum potassium levels in the normal range while treated with sodium zirconium cyclosilicate than while on placebo (80%, 90%, and 94% at the 5 g, 10 g, and 15 g doses, respectively, versus 46% with placebo). An 11-month extension study of the HARMONIZE trial ($n=123$) demonstrated that the treatment effect on serum potassium was maintained during continued therapy.⁵¹

An open-label, 12-month study evaluated the effectiveness of sodium zirconium cyclosilicate 10 g three times daily in 751 hyperkalemic patients (mean baseline serum potassium, 5.6 mEq/L).⁵² Ninety-nine percent of patients achieved normokalemia within 72 hours and were able to enter the maintenance phase, in which patients received 5 g sodium zirconium cyclosilicate with dose adjustments as needed based on serum potassium levels (range, 5 g every other day to 15 g/day). In an 11-month extension study, the effect of sodium zirconium cyclosilicate on serum potassium was maintained throughout the maintenance phase.

DIALIZE: A double-blind, placebo-controlled trial (NCT03303521) evaluated the efficacy of sodium zirconium cyclosilicate in lowering serum potassium in 196 chronic hemodialysis patients with persistent pre-dialysis hyperkalemia (average baseline potassium, 5.8 mEq/L).⁵³ Patients enrolled had an average age of 58 years (range, 20 to 86 years) and were randomized to receive sodium zirconium cyclosilicate 5 grams or placebo once daily on non-dialysis days. During the initial 4 weeks, the dose was adjusted weekly in 5 gram increments up to 15 grams once daily based on pre-dialysis serum potassium measurement after the long interdialytic interval to reach a pre-dialysis serum potassium level of 4 to 5 mEq/L. Following titration, the dose achieved at the end of this timeframe was continued during the subsequent 4-week evaluation period. The primary endpoint assessed was the proportion of responders which was defined as patients who maintained a pre-dialysis serum potassium of 4 to 5 mEq/L on ≥ 3 out of 4 dialysis treatments following the long interdialytic interval and who did not receive rescue therapy during this period. In the sodium zirconium cyclosilicate study group, 41% of patients were responders compared to 1% of placebo patients ($p < 0.001$). Additionally, the treatment effect on average pre-dialysis serum potassium levels continued during treatment.

META-ANALYSES

A systematic review and meta-analysis of phase 2 and 3 clinical trials of patiromer and sodium zirconium cyclosilicate for hyperkalemia included 6 studies.⁵⁴ Although there was significant heterogeneity in the analyses ($I^2 = 80.6\%$ to 99.6%), the authors found a significant reduction in serum potassium with patiromer at 3 days (-0.36 mEq/L; SD range, ± 0.07 to 0.3) and 4 weeks (-0.7 mEq/L; 95% CI, -0.48 to -0.91 mEq/L), as well as a change in serum potassium with sodium zirconium cyclosilicate at 48 hours (-0.67 mEq/L; 95% CI, -0.45 to -0.89). Notably, patiromer was associated with more GI adverse effects and electrolyte depletion while sodium zirconium cyclosilicate was associated with more urinary tract infections and edema.

A 2020 Cochrane review evaluated the benefits and harms of potassium binders for chronic hyperkalemia in CKD patients.⁵⁵ A total of 15 studies evaluating 1,849 adults were selected for inclusion with the majority of studies (12 studies) assessing patients with CKD stage 1 to 5 not requiring dialysis and 3 studies assessing patients requiring dialysis. Studies were required to be either randomized controlled trials or quasi-randomized controlled studies in adults or children with CKD. None of the clinical trials selected for inclusion assessed children, and the average study age ranged from 53.1 years to 73 years. Ten studies compared a potassium binder to placebo, and 3 studies were crossover studies. None of the studies assessed treatment impact for cardiac arrhythmias or major GI events. The overall certainty of evidence was deemed to be low. While the newer agents (patiromer or sodium zirconium cyclosilicate) were found to make little or no difference on death (relative risk, 0.69; 95% CI, 0.11 to 4.32; $I^2 = 0$; low certainty evidence), the effect of older agents (SPS and calcium polystyrene sulfonate [not commercially available in the US]) could not be determined. However, potassium binders were found to potentially lower serum K levels in CKD and hemodialysis patients (3 studies). No difference was found

between high-dose and low-dose patiromer for sudden death (1 study), stroke (1 study), myocardial infarction (1 study), or constipation (1 study). Overall, authors concluded that evidence to aid in clinical decisions for the various potassium binders in this patient population is of low certainty. Due to the paucity of evidence on cardiac arrhythmias or major GI symptoms, a large, well-powered, placebo-controlled study of potassium binders evaluating relevant clinical outcomes would be beneficial.

SUMMARY

Hyperkalemia, despite its variable definition relating to severity, can result in muscle weakness or paralysis, neurologic impairment, cardiac conduction abnormalities, and bradyarrhythmias, particularly in severe cases. Chronic hyperkalemia is often mild or moderate in severity and typically can be managed more slowly by addressing the underlying disorder, dietary potassium intake, use of loop diuretics, adjustment of causative medications, and/or the use of potassium binders. There are 3 agents in the potassium binder class: sodium polystyrene sulfonate (SPS; once marketed under the trade name Kayexalate), patiromer (Veltassa), and sodium zirconium cyclosilicate (Lokelma). While other treatments are approved and/or considered standard of care for the treatment of life-threatening hyperkalemia, potassium binders are approved for the treatment of hyperkalemia only in non-emergency treatment conditions due to their delayed onset of action. This delayed onset of action is a result of their mechanism of action; each results in an increase in potassium excretion via a cation exchange in the gastrointestinal (GI) tract.

All agents in this class should be avoided in patients with bowel disease (e.g., severe constipation, abnormal post-operative motility disorders, and bowel obstruction/impaction) due to the potential effect on GI motility. Cases of intestinal necrosis have been reported with sodium polystyrene sulfonate, most of which involved concomitant use of sorbitol, which is not recommended. It is also contraindicated in neonates with reduced gut motility, although no agent in this class carries an indication in pediatric patients. Non-potassium electrolyte disturbances may also occur with both patiromer (magnesium) and sodium polystyrene sulfonate (magnesium, calcium). Similarly, both sodium polystyrene sulfonate and sodium zirconium cyclosilicate both contain a significant amount of sodium, which could lead to edema in sensitive patients. In clinical trials of the 2 newer agents in this class, patiromer has been most associated with GI adverse effects and reduced magnesium levels while sodium zirconium cyclosilicate has been most associated with edema.

All agents in this class are available as powders for suspension, which require reconstitution in liquid for oral administration. Sodium polystyrene sulfonate may also be administered rectally. The dose is dependent on serum potassium levels and response and should be adjusted to maintain normokalemia. During maintenance treatment, all agents can be dosed once daily. While not absorbed systemically, all agents do carry the risk of drug interactions due to their binding potential and/or potential effect on pH; all agents require dosing precautions for co-administration of other medications ranging from 2 hours to 6 hours.

Head-to-head and rigorous, high-quality, double-blind, randomized clinical trials are limited in this class, and the effectiveness and safety of chronic sodium polystyrene sulfonate use are not well-established in published literature, despite years of its use for hyperkalemia. In addition, recommendations from professional organizations guiding treatment of chronic hyperkalemia are lacking.

REFERENCES

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