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Short Communication

Potassium Binders

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Abstract

Sodium polystyrene sulfonate was approved by the FDA in 1958. It was the only potassium binder available on the market until 2015. Patiromer and sodium zirconium cyclosilicate are newly approved potassium binders. They are better tolerated and can be used on a chronic basis to mitigate hyperkalemia. They allow patients to continue to use critical medications such as ACE inhibitors even in advanced chronic kidney disease.

Keywords: Hyperkalemia; Potassium Disorders; Sodium Polystyrene Sulfonate; Patiromer; Sodium Zirconium Cyclosilicate

1. Introduction

Hyperkalemia can be mild (potassium [K^+] 5.5-5.9), moderate (K^+ 6-6.9) or severe ($K^+ \geq$ 7 mEq/l). Hyperkalemic emergencies (serum K^+ is usually ≥6.0 mEq/l) are seen in patients with rapidly rising K^+ as in rhabdomyolysis. Potentially fatal cardiac arrhythmias can develop. The treatment of these emergencies focuses on myocardial membrane stabilization (intravenous [IV] calcium gluconate or chloride), shifting K^+ intracellularly (IV regular insulin with IV dextrose, nebulized albuterol, and possibly IV sodium [Na^+] bicarbonate), and elimination of K^+ (loop diuretics, hemodialysis, and K^+ binders) [1]. Most K^+ binders have a delayed onset of action and should never be the sole treatment of a hyperkalemic emergency. K^+ binders are used for the management of nonemergent and chronic hyperkalemia. They are combined with dietary counseling, medication adjustments and elimination of K^+ sources such as K^+ supplements and K^+ containing salt substitutes. In this capacity, they enable patients to stay on critical medications such as inhibitors of the renin-angiotensin-aldosterone system (RAAS inhibitors) including angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor

blockers (ARBs) and aldosterone antagonists (such as spironolactone and eplerenone). RAAS inhibitors are crucial in the management of patients with disorders such as systolic heart failure and chronic kidney disease (CKD) with proteinuria. RAAS inhibitors can cause hyperkalemia in patients with CKD resulting in discontinuation or dose reduction which is associated with increased mortality [2]. The newer K^+ binders (patiromer and sodium zirconium cyclosilicate) are better tolerated and more appropriate for chronic use than sodium polystyrene sulfonate, Table 1.

Characteristic	**Sodium polystyrene sulfonate**	**Patiromer**	**Sodium zirconium cyclosilicate**
Brand names	Kayexalte, Kalexate, Kionex	Veltassa	Lokelma
Chemistry	Cation-exchange resin	Polymer	Non-absorbed zirconium silicate
Indication	Treatment of non-emergency hyperkalemia	Treatment of non-emergency hyperkalemia	Treatment of non-emergency hyperkalemia
Mechanism	Na^+ partially released in colon and replaced by K^+. Efficiency of process is limited.	Exchanges Ca^{+2} for K^+ (and Mg^{+2})	Exchanges H^+ and Na^+ for K^+
Warnings	Colon necrosis reported especially with sorbitol	Avoid in severe constipation, or bowel obstruction	Avoid in severe constipation, or bowel obstruction
Onset of action	Hours to days	7 hours	1 hour
Selectivity	Not K^+ selective, can cause hypomagnesemia and hypocalcemia	Binds K^+ and Mg^{+2}	Preferentially captures K^+
Na content	100 mg per g of drug	None	80 mg per g of drug
Precautions	Severe CHF and severe edema. Severe constipation. Avoid use with sorbitol.	Hypomagnesemia	Dose-dependent edema
Drug interactions	Significantly bind to warfarin, metoprolol, furosemide, amoxicillin, amlodipine and phenytoin. Avoid with digoxin (risk of hypokalemia).	Can bind to medications especially ciprofloxacin, levothyroxine and metformin	Transiently increases gastric pH. Can alter absorption of drugs with pH-dependent solubility such as furosemide, atorvastatin and dabigatran.
Dosage	15g (1-4 times/day) orally. 30-50 g enema q 6 h	8.4 g once daily. Max: 25.2 g once daily	Loading: 10 g tid x 48 h. Maintenance: 5-15 g daily

Table 1: Comparison of available potassium binders.

2. Sodium Polystyrene Sulfonate (SPS)

SPS is a non-absorbed cation-exchange resin that was approved by the FDA in 1958. The recommended dose is 15-60 g given as a 15 g dose 1-4 times daily. It is the only binder that can be given as a rectal enema. The dose is 30-50 g every 6 hours rectally. SPS should be given at least 3 h before or 3 h after other oral drugs to avoid binding of these medications. 15 g of SPS contains about 60 mEq (1500 mg) of Na^+, therefore, it should be given with caution to patients with severe heart failure or severe edema [3]. Intestinal necrosis (occasionally fatal) has been reported with SPS especially when used with sorbitol. SPS should not be used with sorbitol and should also be avoided in patients who have not had a bowel movement after surgery and in patients at risk of for constipation or fecal impaction.

Patients with history of inflammatory bowel disease, ischemic colitis and bowel resection are not appropriate candidates for the use of SPS. SPS is not specific for K^+, it can bind calcium (Ca^{+2}) and magnesium (Mg^{+2}). SPS should not be used with cation-containing antacids such Mg^{+2} hydroxide due to the risk of metabolic alkalosis and reduction of K^+ exchange. SPS exchange ratio is 1mEq of K^+ per 1 g of resin. Since the efficiency of Na^+-K^+ exchange is 33%, approximately one-third of the Na^+ in SPS is absorbed. After K^+ exchange, SPS is excreted in the stool and is not absorbed systematically. Long-term studies involving SPS are very limited [4]. A retrospective observational study in 26 patients with stage 3-4 CKD evaluated the use of low-dose SPS in mild chronic hyperkalemia. SPS was well-tolerated and effective over a median follow up of 15.4 months [5]. Another retrospective study in 14 patients with CKD and heart disease on RAAS inhibitors, also demonstrated the safety and efficacy of low-dose SPS over a median follow up of 14.5 months [6].

3. Patiromer

Patiromer was approved by the FDA in 2015. It is a non-absorbed K^+ binding polymer that exchanges Ca^{+2} for K^+. The active ingredient is patiromer sorbitex calcium [7]. The most common adverse reactions are gastrointestinal (GI) including constipation in 7.2% and diarrhea in 4.8%. Serum Mg^{+2} should be monitored because patiromer binds Mg^{+2} in the colon. Hypomagnesemia was reported in 5.3% of patients and hypokalemia in 4.7% of patients. As is the case with SPS, patiromer should be avoided in patients with bowel obstruction, severe constipation and post-surgical patients who have not had a bowel movement. Most of the patients in clinical trials involving patiromer had CKD. Patiromer increases fecal excretion of K^+ by binding in the GI lumen. Patiromer is available as a powder for oral suspension and should be refrigerated at 2°C to 8°C. It is mixed and completely stirred with 90 ml of water and then taken immediately with food once daily. Initial dose is 8.4 g once daily and can be increased by 8.4 g increments weekly to a maximum of 25.2 g once daily. Patiromer should not be heated or added to heated liquids. As is the case with SPS, patiromer should be given at least 3 h before or 3 h after other oral drugs to avoid binding of these medications. Patiromer significantly binds the following medications: metformin, levothyroxine and ciprofloxacin [8]. Several clinical trials demonstrated the efficacy and safety of patiromer. In the AMETHYST-DN study [9], patients on patiromer maintained their K^+ in the normal range over 52-weeks. This phase 2 trial included 306 patients with type II DM and CKD (eGFR 15-59 ml/min/1.73 m^2). All patients were on RAAS inhibitors and had K^+> 5 mEq/l. About a third had NYHA class I or II heart failure. The OPAL-HK trial included patients with CKD on RAAS inhibitors [10]. Treatment with patiromer lead to maintenance of K^+ in the normal range.

Approximately one-half of the patients on placebo had to discontinue RAAS inhibitors in this 12-week study. Other clinical trials with patiromer are ongoing.

4. Sodium Zirconium Cyclosilicate (SZC)

SZC was approved by the FDA in 2018. It is a non-absorbed zirconium silicate that exchanges H^+ and Na^+ for K^+. SZC has high affinity for capturing K^+ compared to other cations such as Ca^{+2} and Mg^{+2}. K^+ is captured in the GI tract and is excreted in the stool [11]. SZC should be given at least 2 h before or 2 h after other oral drugs to avoid binding of these medications. SZC transiently increases gastric pH and can alter absorption of drugs with pH-dependent solubility such as furosemide, atorvastatin and dabigatran. As is the case with SPS and patiromer, SZC should be avoided in patients with bowel obstruction, severe constipation and post-surgical patients who have not had a bowel movement. Each 5 g dose of SZC contains 400 mg of Na^+. SZC has been associated with mild to moderate dose-dependent edema. Volume overload does not seem to be a major concern [12]. SZC starting dose is 10 g three times a day for up to 48 h. The maintenance dose is 5-15 g daily. SZS does not require refrigeration. It is available as a powder that is stirred with ≥ 45 ml of water and drunk immediately. Several phase 2 and phase 3 trials demonstrated the safety and efficacy of SZC in the management of chronic hyperkalemia especially in CKD patients on RAAS inhibitors [12, 13]. The onset of action was 1 h after the first 10 g dose. Gastrointestinal adverse reactions were comparable to placebo. The DIALIZE study demonstrated the safety and efficacy of SZC for the treatment of predialysis hyperkalemia in patients with end-stage renal disease on hemodialysis [14]. Given SZC rapid onset of action, it is being investigated for the management of emergency hyperkalemia (ENERGIZE study ClinicalTrials.gov Identifier: NCT03337477).

5. Conclusion

- Potassium binders should never be the sole treatment of hyperkalemic emergencies.
- Patiromer and sodium zirconium cyclosilicate are newly approved potassium binders for treatment of chronic hyperkalemia. They are better tolerated, better studied, and more suited for chronic use than sodium polystyrene sulfonate.
- New potassium binders allow continuation of critical medications that are often discontinued in advanced chronic kidney disease due to hyperkalemia. Discontinuation or dose reduction of such medications is associated with increased morbidity and mortality.
- The new potassium binders are being studied in dialysis patients. Their use may help in reducing the use of low K^+ baths in hemodialysis (K^+ bath < 2.0), and subsequently reduce the incidence of cardiac arrythmias in hemodialysis patients.

Conflicts of Interest

The author declares no conflict of interest.

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