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ORIGINAL ARTICLE

Treatment of infant formula with patiromer dose dependently decreases potassium concentration

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Abstract

Background Hyperkalemia is a potentially life-threatening complication of chronic kidney disease (CKD). Dietary potassium restriction is challenging in infants despite low-potassium formulas. Decreasing potassium in formula using patiromer, a new calcium-based cation exchange polymer may be one option to accomplish this; however, data confirming efficacy is lacking.

Methods Varying doses of patiromer were added to prepared Similac Advance and Similac PM 60/40. Measurements of potassium, calcium, sodium, magnesium, and phosphorus were obtained at baseline and at 30 min, 60 min, and 24 h following patiromer administration.

Results Following pre-treatment with patiromer, the potassium concentration of both formulas decreased. This effect was mild with the lowest dose but increased in a dose-dependent fashion. Treating for 60 min or 24 h did not yield substantially greater effects than treating for 30 min. Calcium levels increased in both formula groups, mostly in a dose-dependent fashion. Changes in magnesium, sodium, and phosphorus were also seen after patiromer pre-treatment.

Conclusions Pre-treatment with patiromer decreases the potassium concentration of infant formula. Calcium levels increased after treatment as expected with the majority of ion exchange occurring in 30 min. Treatment of formula with patiromer shows promise as a unique option for managing hyperkalemia.

Keywords Patiromer · Potassium · Hyperkalemia · Formula

Introduction

One of the challenges of caring for infants with chronic kidney disease (CKD) or end-stage renal disease (ESRD) is the optimal delivery of nutrition while preventing electrolyte abnormalities including hyperkalemia. Hyperkalemia is a common complication in this patient population and the prevalence increases significantly with declining glomerular filtration rate (GFR) [1, 2]. There are many etiologies for the development of hyperkalemia in children with CKD including inadequate potassium filtration and excretion, metabolic acidosis, aldosterone resistance from urinary obstruction, and treatment with medications such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers [3]. Treatment for hyperkalemia typically starts with limiting potassium intake, but this can be difficult for children with CKD who typically need increased calories given their high risk for poor growth [4].

The use of sodium polystyrene sulfonate (SPS), a cation exchange resin, is a well-established therapy both for the treatment and prevention of hyperkalemia in patients with CKD [5]. However, specific adverse effects of either oral or rectal administration of SPS have been observed in the infant population including hypernatremia, intestinal obstruction, necrotizing enterocolitis, and bowel perforation [6–8]. Additionally, there are reports of SPS obstructing enteral feeding tubes, which neonates with CKD often require for both nutrition and medication delivery [9]. For these reasons, its use is contraindicated in neonates. Pre-treating formula with sodium polystyrene sulfonate and decanting the resin is one strategy for removing potassium from an infant's diet while still supplying adequate nutrition. While this strategy is effective in reducing serum potassium levels, it delivers a very significant

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sodium load which may not be well tolerated in the infant with CKD or ESRD [10, 11].

Patiromer, a calcium-based cation exchange medication, was FDA approved in 2015 for the treatment of hyperkalemia in adults; however, its safety and efficacy have not been established for pediatric patients. Using patiromer to pre-treat infant formula may be one novel therapy to treat hyperkalemia in infants with CKD or ESRD without exposing the patients directly to the drug. While this may be an alternative to pre-treating formula with SPS, no studies have demonstrated that patiromer will decrease the potassium content of infant formula. The aim of this study was to determine if patiromer is effective in reducing the potassium concentration of infant formula and to evaluate the effect of differing doses on potassium reduction. A secondary aim was to assess the effect of non-targeted ion exchange.

Methods

Similac Advance (SA) and Similac PM 60/40 (SPM) powder concentrates were obtained and mixed with water according to the package directions. Six total containers (three of each type of formula) were prepared to a total volume of 500 ml each and kept refrigerated (37 °F/3 °C). Fifteen-milliliter samples were taken from each container at baseline. Patiromer granules were added to the containers of SA or SPM in doses of 2.1 g, 8.4 g, or 16.8 g. All patiromer used in this study was obtained from 8.4-g packets. For the 2.1-g dose, the amount of patiromer was weighed on a laboratory scale to 2.1 g. The 8.4-g dose was added as a single packet and the 16.8-g dose was added as two 8.4-g packets. The granules were stirred into the formula for 60 s and returned to the refrigerator. Fifteen-milliliter samples were again taken at 30 min, 60 min, and 24 h. All samples were kept refrigerated until sent for analysis. Once all samples were collected, they were analyzed by inductively coupled plasma optical emission spectrometry by Dr Ibrahim Saeed for mineral and electrolyte content at Soilnet LLC (Madison, WI).

Additionally, 12-ml samples of formula were obtained and 2.1 g of patiromer were added to these test tubes and shaken thoroughly. They were allowed to sit upright and monitored for visual signs of sediment precipitating at the bottom of the test tube.

Results

Mineral and electrolyte concentrations for the formula samples before and after patiromer treatment are highlighted in Table 1. Measured potassium concentrations of almost all of the patiromer-treated samples decreased when compared with the pre-treatment potassium levels of the equivalent formula type. The degree of potassium decrease was seen in a dose-dependent fashion (Fig. 1). The largest decrease in potassium levels was seen in the SA formula treated with 16.8 g which started with a pre-treatment potassium concentration of 83.00 mg/dl and decreased to 38.11 mg/dl after 24 h of treatment with patiromer, a 54% decrease. The lowest final potassium levels were seen in the SPM formula treated with 16.8 g which began with a pre-treatment potassium concentration of 41.90 mg/dl and decreased to 31.06 mg/dl after 24 h of treatment with patiromer, which is a 26% decrease from pre-treatment levels. In all studies, the largest drop in potassium was seen at the 30-min mark and smaller decreases were seen subsequently at 60 min and 24 h as shown.

Calcium concentrations increased in a similar manner. Calcium levels consistently increased after treatment with patiromer and did so in a dose-dependent fashion (Fig. 2). The highest calcium increases and the highest calcium levels were seen in the SA formula treated with 16.8 g. Again, the largest increase in calcium concentration was seen after 30 min of treatment with much smaller increases at 60 min and 24 h.

Magnesium levels also decreased in all formulas treated with patiromer in a dose-dependent manner (Fig. 3). Sodium concentrations decreased slightly following treatment with patiromer. Phosphorus concentrations increased slightly and this was again seen in a dose-dependent manner.

On visual inspection, patiromer precipitated to the bottom of the formula suspension in separate test tubes. This had maximum effect by 2–3 min. See Fig. 4 for patiromer precipitation at 3 min after addition of patiromer to the formula.

Discussion

We have demonstrated that patiromer is effective at reducing the potassium content of two types of infant formulas, Similac Advance, and the lower mineral formula Similac PM 60/40. The underlying principal of pre-treating formula is not unique as it was first noted in 1972 by *Starbuck* that sodium polystyrene sulfonate (SPS) effectively decreased the potassium content of cow's milk. Later, Bunchman et al. described a similar set of experiments where SPS also decreased the potassium content of various liquids including the infant formula Similac PM 60/40 [11]. Utilizing these techniques, the infant receives the lower potassium formula that has been pre-treated with SPS but does not receive the drug itself as the SPS is discarded after cation exchange occurs but prior to the infant receiving the formula. This is an effective way to manage hyperkalemia in infants with renal insufficiency as demonstrated by Thompson et al. [10]. While pre-treating formula with SPS is standard practice for treating hyperkalemia in infants, it still delivers a high sodium load to patients at risk for hypervolemia and in suspension form can increase the

Table 1 Changes in electrolyte and mineral concentrations with patiromer-treated formula

Formula—patiromer dose (time)	K (mg/dl)/ (mEq/l)	Ca (mg/dl)/ (mEq/l)	Mg (mg/dl)/ (mEq/l)	Na (mg/dl)/ (mEq/l)	P (mg/dl)/ (mEq/l)
SA—2.1 g (0)	79.74/20.45	55.27/27.64	8.19/6.74	17.87/7.77	49.35/31.84
SA—2.1 g (30)	74.81/19.18	56.47/28.24	7.39/6.08	17.03/7.40	52.99/34.19
SA—2.1 g (60)	73.78/18.92	59.52/29.76	6.76/5.56	17.2/7.48	55.68/35.92
SA—2.1 g (24)	75.56/19.37	62.34/31.17	6.73/5.54	17.8/7.74	59.51/38.39
SA—8.4 g (0)	80.67/20.68	55.40/27.70	8.02/6.60	18.05/7.85	49.94/32.22
SA—8.4 g (30)	61.7/15.82	78.94/39.47	7.62/6.27	16.79/7.30	54.45/35.13
SA—8.4 g (60)	61.58/15.79	82.86/41.43	5.33/4.39	16.75/7.28	58.32/37.63
SA—8.4 g (24)	58.46/14.99	86.66/43.33	5.42/4.46	16.96/7.37	63.78/41.15
SA—16.8 g (0)	83.05/21.28	53.33/26.67	8.30/6.83	20.15/8.76	51.75/33.39
SA—16.8 g (30)	41.00/10.51	80.81/40.41	3.10/2.55	16.46/7.16	53.97/34.82
SA—16.8 g (60)	45.76/11.73	81.98/40.99	3.43/2.82	17.24/7.50	63.74/41.12
SA—16.8 g (24)	38.11/9.77	87.80/43.90	2.40/1.98	15.19/6.60	65.13/42.02
SPM—2.1 g (0)	43.81/11.23	36.98/18.49	7.79/6.41	14.29/6.21	32.21/20.78
SPM—2.1 g (30)	46.68/11.97	39.11/19.56	7.5/6.17	14.77/6.42	33.35/21.52
SPM—2.1 g (60)	45.50/11.67	41.40/20.70	7.21/5.93	14.96/6.50	36.7/23.68
SPM—2.1 g (24)	42.19/10.82	40.34/20.17	6.33/5.21	14.22/6.18	36.64/23.64
SPM—8.4 g (0)	42.97/11.02	37.35/18.68	7.33/6.03	14.80/6.43	33.67/21.72
SPM—8.4 g (30)	44.28/11.35	50.97/25.49	5.32/4.38	14.31/6.22	38.56/24.88
SPM—8.4 g (60)	39.76/10.19	50.29/25.15	5.26/4.33	14.18/6.17	39.83/25.70
SPM—8.4 g (24)	37.75/9.68	50.34/25.17	6.03/4.96	14.28/6.21	39.23/25.31
SPM—16.8 g (0)	41.90/10.74	36.77/18.39	6.98/5.74	14.95/6.50	32.71/21.10
SPM—16.8 g (30)	33.36/8.55	56.94/28.47	4.91/4.04	13.87/6.03	39.52/25.50
SPM—16.8 g (60)	33.88/8.69	57.38/28.69	4.47/3.68	14.09/6.13	40.16/25.91
SPM—16.8 g (24)	31.06/7.96	56.24/28.12	3.69/3.04	14.48/6.30	35.59/22.96

SA, Similac Advance; *SPM*, Similac PM 60/40; *0*, pre-patiromer; *30*, 30 min; *60*, 60 min; *24*, 24 h; *K*, potassium; *Ca*, calcium; *Mg*, magnesium; *Na*, sodium; *P*, phosphorus. Solute concentrations are expressed in mg/dl and mEq/l.

aluminum content of the formula in patients already at high risk for heavy metal toxicity [12]. There are also frequent occurrences of hypokalemia, hypernatremia, and hypocalcemia seen in infants who receive SPS treated formula [13]. Calcium polystyrene sulfonate may be in theory more effective at potassium removal, due to its divalent exchange potential, as well as better tolerated; however, it is not available in the USA. With the introduction of patiromer, we now have the possibility to effectively pre-treat infant formulas with a calcium-based cation exchanger, avoiding the ill effects associated with SPS.

Patiromer, a calcium-based cation exchange polymer, has been proven to be an effective therapy for the prevention and treatment of chronic hyperkalemia in adults. This was initially demonstrated in heart failure patients who had a history of hyperkalemia secondary to medications that interfere with potassium homeostasis or patients with co-morbid CKD [14]. Subsequently, this was confirmed in hyperkalemic adults with CKD either on renin-angiotensin-aldosterone inhibitor or with diabetic kidney disease [15, 16] with FDA approval for its use granted in 2015. Despite this, it is not yet approved for use in children with CKD.

To lower the potassium content of formula without exposing children to patiromer, we treated infant formula with patiromer and decanted the formula after allowing ion exchange to take place. Patiromer has not been approved for pediatric use and there are no recommendations regarding appropriate patiromer dosing for children. For adults greater than 18 years old, the suggested doses include either 8.4 g once daily, 16.8 g once daily, or 25.2 g once daily. Subsequently, it is commercially available in packets containing 8.4 g, 16.8 g, or 25.2 g of medication. The patiromer product is a 100-μm bead with numerous beads in each packet; therefore, for this experiment, we used the starting and middle adult doses given their ease of use in adding packets or multiples of packets to the formula. As these doses are daily doses for an adult, we hypothesized that there may be excess potassium removal in adding these doses to an infant's daily formula requirement. The 2.1-g dose was chosen to try and better approximate an infant's or child's daily patiromer dose.

After demonstrating that the patiromer separates quickly from the formulas, we found that patiromer removes potassium from both Similac Advance and Similac PM 60/40 in a dose-dependent fashion. At the highest doses

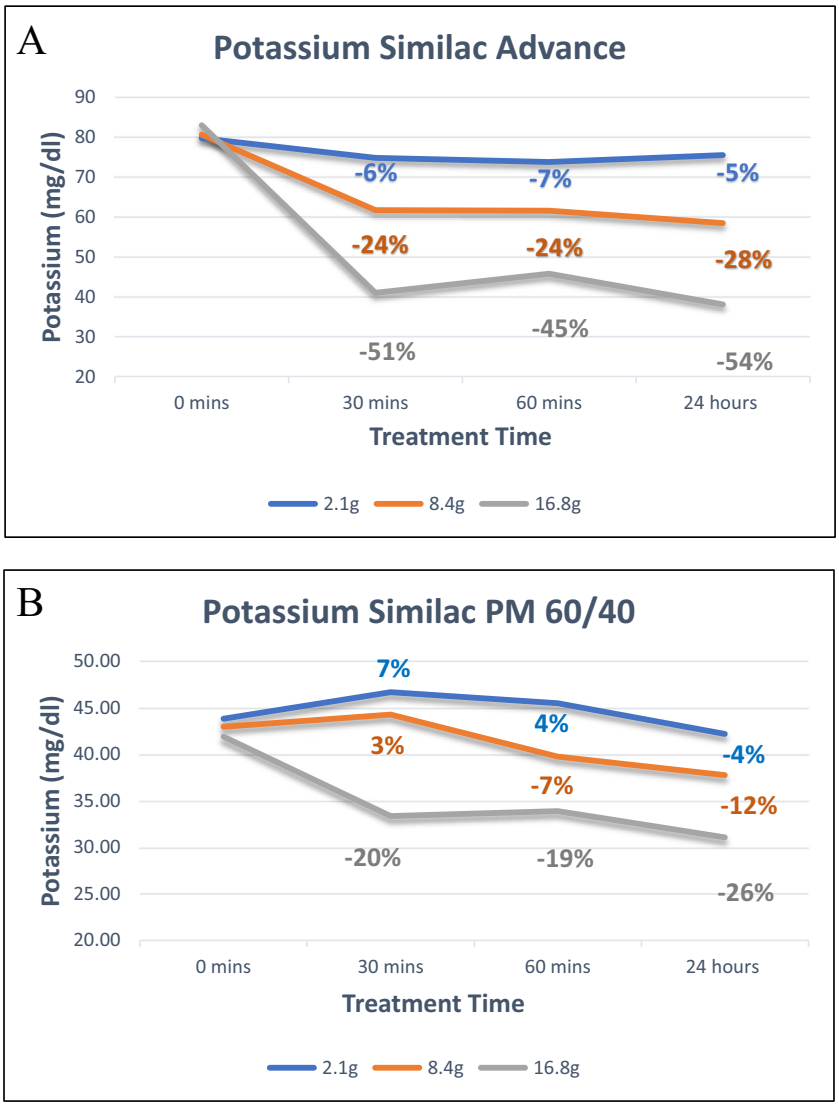

Fig. 1 Changes in potassium concentrations with patiromer-treated formula. **a** Decreases in the potassium content of Similac Advance; **b** decreases in the potassium content of Similac PM 60/40. The potassium content decreases in both formulas following treatment with patiromer, seen dose-dependently. Percentages note change from baseline

tested, the potassium content of Similac Advance and Similac PM 60/40 decreased by 51% and 20% respectively after 30 min of treatment with 16.8 g of patiromer. This represents a potentially significant decrease to dietary potassium intake in children who require a potassium-limited diet. This will allow full delivery of nutrition and calories without fear of causing hyperkalemia in infants and children with decreased renal function. Furthermore, the potassium depletion happens relatively rapidly, allowing for short preparation times when pre-treating this formula for infants. We did not treat formula with higher doses, such as 25.2 g, but it is possible that even higher doses may result in even more effective potassium removal. This will need to be evaluated in future in vitro or clinical experiments.

The patiromer induced potassium depletion correlates with an increase in the calcium content of the formulas, indicating that successful cation exchange is occurring. Again, the amount of calcium in the decanted formula increased in a dose-dependent manner as more patiromer was added. This could prove advantageous as the extra calcium could potentially serve as a phosphate binder for those children inclined to develop hyperphosphatemia, as suggested by the fact that the calcium in patiromer has been shown to decrease intestinal phosphorus absorption in healthy volunteers and in hemodialysis patients [17, 18]. Of course, it is unclear if the same mechanism will be demonstrated when the medication is used to treat formula as opposed to given per os and will be important to follow phosphorus levels clinically if patiromer-treated formula is given to infants. It will also be essential to make sure that these children with chronic kidney disease are not receiving excessive calcium, as this has been implicated in the progression of arterial calcification [19].

As patiromer is a non-selective ion exchanger, there is the possibility that ions other than potassium will be affected by using patiromer to treat infant formulas. We demonstrated a

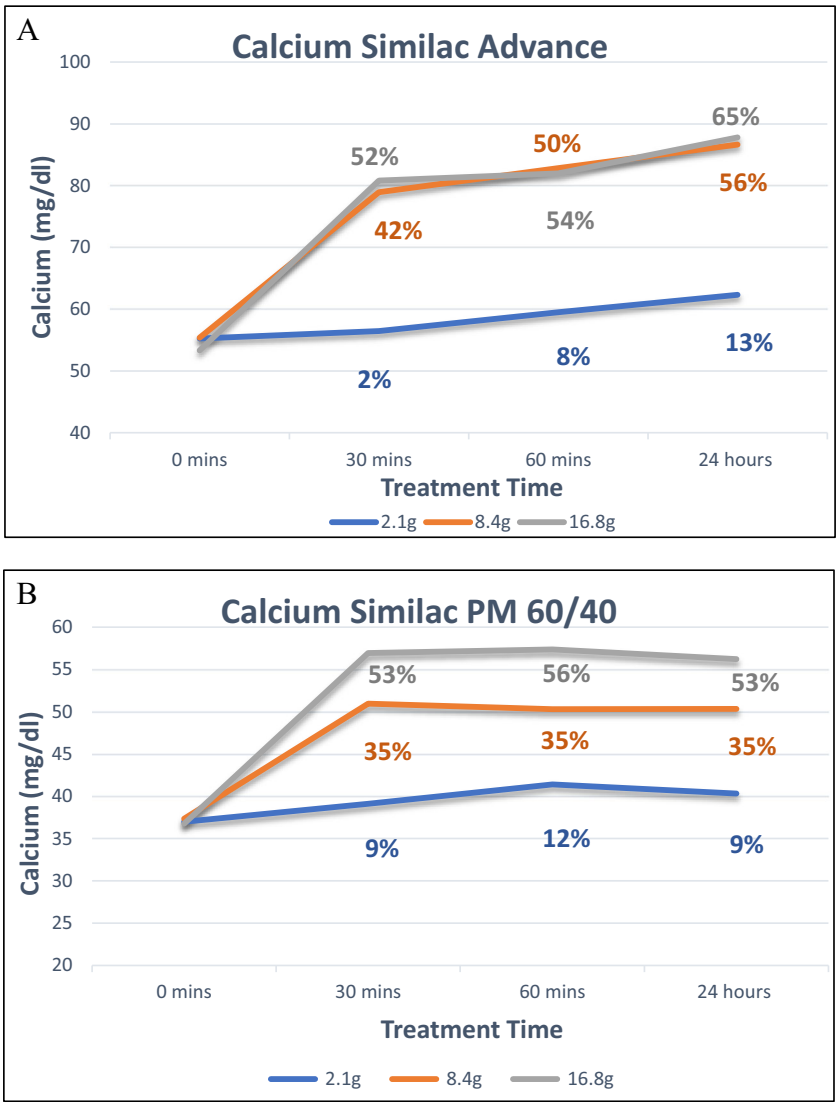

Fig. 2 Changes in calcium concentrations with patiromer-treated formula. **a** Increases in the calcium content of Similac Advance; **b** increases in the calcium content of Similac PM 60/40. The calcium content increases in both formulas following treatment with patiromer, seen dose-dependently. Percentages note change from baseline

considerable decrease in the magnesium concentration of the formulas treated, with up to a 71% decrease in the Similac Advance formula treated with 16.8 g of patiromer. Comparably, low serum magnesium levels were observed in clinical trials of adults using patiromer, with up to 24% of study participants developing hypomagnesemia [14–16]. This is important to note as children on patiromer-treated formula may require additional magnesium supplementation. Sodium content of the patiromer-treated formulas decreased slightly, especially in the higher sodium Similac Advance. Of course, this is in contrast to SPS-treated formula in which the sodium content increases up to 500% [11]. In addition, patiromer may decrease the concentrations of other cations such as copper, manganese, and zinc. The effect of patiromer on these cations has not been studied comprehensively in clinical studies and was not analyzed in our study, but the clinician using patiromer to treat formula must be aware of the possibility of these nutrient deficiencies.

Surprisingly, the phosphorus concentration of the patiromer-treated formula did increase somewhat. While it is unclear that this is a clinically significant amount, it is concerning given that this therapy will be used in infants and children who are at risk for hyperphosphatemia. Furthermore, the cause of the increased phosphorus is unclear. Patiromer does not contain any phosphates or any elemental phosphorus and while it is possible that changing the cation concentration of the formula could alter the concentration of free phosphates, the assay utilized in this experiment measured total inorganic phosphorus; the amount of free phosphates should not affect the results. Also, it is possible that the increased phosphorus is due to the release of phosphorus from insoluble tricalcium phosphates contained within micelles. The addition of patiromer likely would have changed the pH of the formula causing dissociation of the micelles and an increase in the measured calcium and phosphorus content of the treated formula [20]. Unfortunately, the pH of our

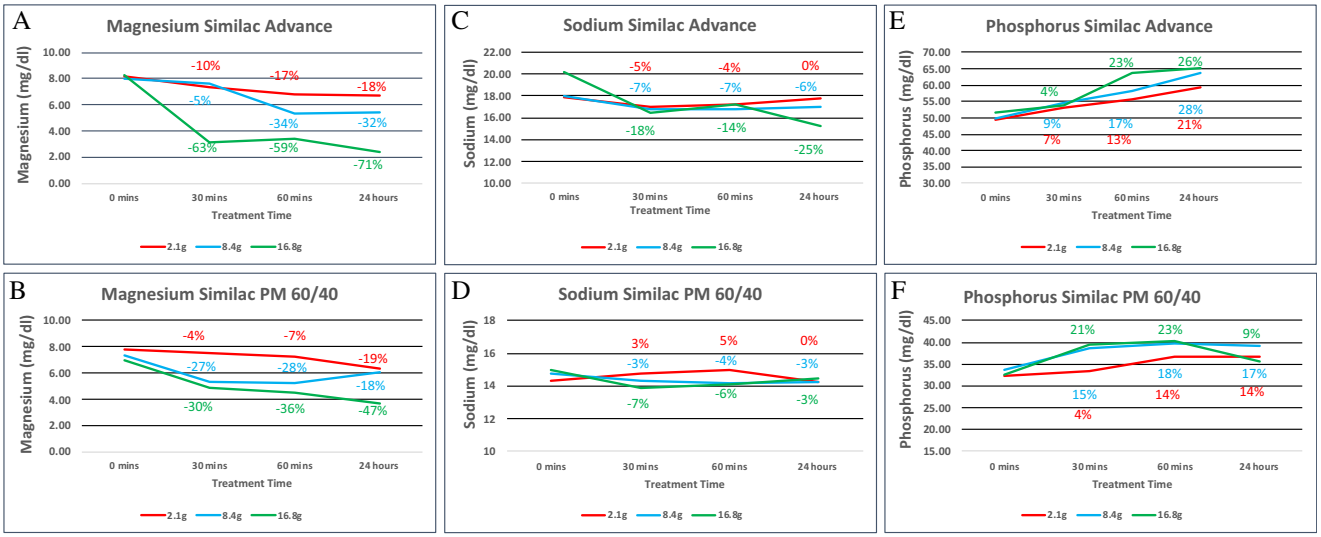

Fig. 3 Changes in non-targeted ion concentrations with patiromer-treated formula. **a** Decreases in the magnesium content of Similac Advance; **b** decreases in the magnesium content of Similac PM 60/40; **c** decreases in the sodium content of Similac Advance; **d** decreases in the sodium content of Similac PM 60/40; **e** increases in the phosphorus content of Similac Advance; **f** increases in the phosphorus content of Similac PM 60/40. Percentages note change from baseline

samples was not measured and the phosphorus content was not analyzed using an ash method, which may have yielded a constant amount of phosphorus in our samples before and after the addition of patiromer. These will be important experiments to carry out in future studies. Interestingly, SPS was noted to increase the phosphorus concentration of Similac PM 60/40 when studied by Taylor et al., although this never reached statistical significance [12]. It will be important to determine the serum and urine phosphorus levels in infants who receive this therapy to see if it truly increases phosphorus delivery in a clinically meaningful way.

Unlike SPS, which is supplied either as a suspension or a powder, the patiromer is a collection of many 100-μm beads. It was not known whether or not patiromer would remain suspended in the formula or would precipitate to the bottom of the container via gravity as SPS does. If the patiromer remained suspended in the formula, it could prove too difficult to separate out the medication from the formula; this process must be simple enough for a parent to perform, but must ensure that the child does not ingest the drug. Fortunately, the patiromer beads are pink in color and were distinctly observed separating out from the formula and falling to the bottom of the container and test tube within 3 min. Since the precipitation of patiromer was relatively quick, one possible advantage to using patiromer to lower the potassium concentration of formulas is that the provider or caregiver preparing the formula may not have to wait 30–60 min to decant the formula after adding patiromer, which is a common protocol for many centers using SPS-treated formula. Unfortunately, not knowing if patiromer would be effective whatsoever in reducing the potassium content of formula, we did not take measure the potassium concentration of the treated formula at 3 min. This is something that should be examined in future studies; if successful, this could save several hours per week in preparing patiromer-treated formula.

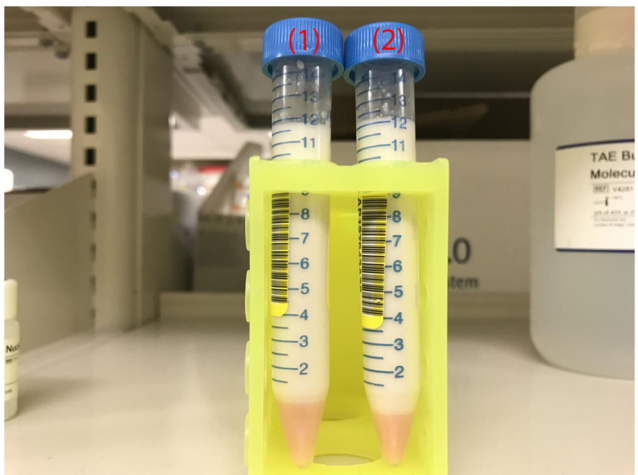

Fig. 4 Precipitation of patiromer in formula. **a** Patiromer (pink) settling to bottom of Similac Advance after 3 min; **b** patiromer (pink) settling to bottom of Similac PM 60/40 after 3 min

Providing adequate nutrition to infants and young children with CKD can be challenging due to the risk for hyperkalemia. Pre-treating formula with SPS has become a standard therapeutic option for the pediatric nephrologist, but this comes with many potential side effects. We have demonstrated that patiromer is successful in dose-dependently lowering the potassium concentration of two common infant formulas. As patiromer is calcium-based, it will increase the calcium delivery of the formula and will alter the concentration of other ions including magnesium, sodium, and phosphorus. Our results suggest that treating formula with 16.8 g of patiromer per 500 ml of formula with a treatment

time of 30 min yields desirable results that could be translated to clinical practice. As a new alternative to SPS, treating formula with patiromer is an attractive option for preventing or treating hyperkalemia in infants and children with poor kidney function. Future studies are needed to determine if this is tolerated and efficacious in children.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Furth SL, Abraham AG, Jerry-Fluker J, Schwartz GJ, Benfield M, Kaskel F, Wong C, Mak RH, Moxey-Mims M, Warady BA (2011) Metabolic abnormalities, cardiovascular disease risk factors, and GFR decline in children with chronic kidney disease. Clin J Am Soc Nephrol 6:2132–2140
2. Wong H, Mylrea K, Feber J, Drukker A, Filler G (2006) Prevalence of complications in children with chronic kidney disease according to KDOQI. Kidney Int 70:585–590
3. Group KW (2009) KDOQI clinical practice guideline for nutrition in children with CKD: 2008 update. Executive summary. Am J Kidney Dis 53:S11–S104
4. Seikaly MG, Salhab N, Gipson D, Yiu V, Stablein D (2006) Stature in children with chronic kidney disease: analysis of NAPRTCS database. Pediatr Nephrol 21:793–799
5. Scherr L, Ogden DA, Mead AW, Spritz N, Rubin AL (1961) Management of hyperkalemia with a cation-exchange resin. N Engl J Med 264:115–119
6. Ohlsson A, Hosking M (1987) Complications following oral administration of exchange resins in extremely low-birth-weight infants. Eur J Pediatr 146:571–574
7. Filippi L, Cecchi A, Dani C, Bertini G, Pezzati M, Rubaltelli FF (2004) Hypernatraemia induced by sodium polystyrene sulphonate (Kayexalate) in two extremely low birth weight newborns. Paediatr Anaesth 14:271–275
8. Harel Z, Harel S, Shah PS, Wald R, Perl J, Bell CM (2013) Gastrointestinal adverse events with sodium polystyrene sulfonate (Kayexalate) use: a systematic review. Am J Med 126:264 e269–264 e224
9. Wood EG, Bunchman TE, Khurana R, Fleming SS, Lynch RE (1990) Complications of nasogastric and gastrostomy tube feedings in children with end stage renal disease. Adv Perit Dial 6:262–264
10. Thompson K, Flynn J, Okamura D, Zhou L (2013) Pretreatment of formula or expressed breast milk with sodium polystyrene sulfonate (Kayexalate((R))) as a treatment for hyperkalemia in infants with acute or chronic renal insufficiency. J Ren Nutr 23:333–339
11. Bunchman TE, Wood EG, Schenck MH, Weaver KA, Klein BL, Lynch RE (1991) Pretreatment of formula with sodium polystyrene sulfonate to reduce dietary potassium intake. Pediatr Nephrol 5:29–32
12. Taylor JM, Oladitan L, Carlson S, Hamilton-Reeves JM (2015) Renal formulas pretreated with medications alters the nutrient profile. Pediatr Nephrol 30:1815–1823
13. Le Palma K, Pavlick ER, Copelovitch L (2018) Pretreatment of enteral nutrition with sodium polystyrene sulfonate: effective, but beware the high prevalence of electrolyte derangements in clinical practice. Clin Kidney J 11:166–171
14. Pitt B, Anker SD, Bushinsky DA, Kitzman DW, Zannad F, Huang IZ, Investigators P-H (2011) Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. Eur Heart J 32:820–828
15. Bakris GL, Pitt B, Weir MR, Freeman MW, Mayo MR, Garza D, Stasiv Y, Zawadzki R, Berman L, Bushinsky DA, Investigators A-D (2015) Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease: the AMETHYST-DN randomized clinical trial. JAMA 314:151–161
16. Weir MR, Bakris GL, Bushinsky DA, Mayo MR, Garza D, Stasiv Y, Wittes J, Christ-Schmidt H, Berman L, Pitt B, Investigators O-H (2015) Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. N Engl J Med 372:211–221
17. Bushinsky DA, Rossignol P, Spiegel DM, Benton WW, Yuan J, Block GA, Wilcox CS, Agarwal R (2016) Patiromer decreases serum potassium and phosphate levels in patients on hemodialysis. Am J Nephrol 44:404–410
18. Bushinsky DA, Spiegel DM, Gross C, Benton WW, Fogli J, Hill Gallant KM, Du Mond C, Block GA, Weir MR, Pitt B (2016) Effect of patiromer on urinary ion excretion in healthy adults. Clin J Am Soc Nephrol 11:1769–1776
19. Russo D, Corrao S, Battaglia Y, Andreucci M, Caiazza A, Carlomagno A, Lamberti M, Pezone N, Pota A, Russo L, Sacco M, Scognamiglio B (2011) Progression of coronary artery calcification and cardiac events in patients with chronic renal disease not receiving dialysis. Kidney Int 80:112–118
20. Dalgleish DG, Law AJR (1989) pH-Induced dissociation of bovine casein micelles. II. Mineral solubilization and its relation to casein release. J Dairy Res 56:727–735