



EDITORIAL COMMENT

Let food be thy medicine and medicine be thy food?

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Abstract

Ensuring adequate nutrition in children with chronic kidney disease whilst avoiding hyperkalaemia can be a difficult balance to achieve. Pre-treatment of feeds, whether milk, formula or enteral nutrition, with sodium polystyrene sulfonate (SPS) is practiced in some paediatric centres internationally. Such treatments are purported to avoid the potentially serious complications of direct administration of SPS, such as intestinal necrosis, aspiration pneumonitis and metabolic alkalosis to name but a few. Although described some 45 years ago, this study by Palma *et al.* is only the second retrospective study to describe the clinical consequence of pre-treating feeds with SPS with the majority of earlier studies describing only the *in vitro* effects of this method. Whilst effective in reducing serum potassium, the authors justifiably highlight the high incidence of complications, such as hypokalaemia (31.6%) and hypernatraemia (26.3%). We have further highlighted this with a summary of the available literature on this subject demonstrating the gross alterations of the electrolyte composition of feeds following SPS pre-treatment and clinical complications in its application. We heartily agree and support the conclusion by Palma *et al.* that where this therapy is practiced, close monitoring of electrolytes is essential and much more work is needed to identify those patient cohorts for which this can indeed be considered a safe and effective intervention.

Ensuring adequate nutrition is one of the cornerstones of management in children with chronic kidney disease (CKD). Poor nutrition is not only a prime aetiology of delayed growth and short stature but also exacerbates the fluid and electrolyte abnormalities already present in children with CKD [1]. Impaired growth is associated with increased morbidity and mortality both as a child and into adulthood, including the psychological implications to the child of being smaller than his/her peers, increased school absenteeism and more frequent hospital admissions [1]. Several other important complications of CKD may be exacerbated by poor nutrition, including but not limited to electrolyte disturbances (most notably hyperkalaemia), poorer bone health (secondary to calcium and phosphate imbalance) and anaemia [1, 2]. Dietary restrictions are used to address many of these issues. However, maintaining adequate

nutrition and managing often suboptimal poor patient/family concordance with these restrictions remains challenging.

In the context of hyperkalaemia, simple dietary restriction is often inadequate to maintain serum potassium within an acceptable range. Ion exchange resins are commonly used as an adjunctive therapy. Sodium polystyrene sulphonate (SPS), a commonly available exchange resin, can be administered either orally or rectally [3]. However, the reported adverse effect profile includes potentially fatal gastrointestinal side effects such as intestinal necrosis [3–5], aspiration pneumonitis [6, 7], metabolic alkalosis with subsequent seizures [3, 8], palatability [9] and blockage of feeding routes by SPS [10]. It has therefore been suggested that enteral nutrition could be pretreated with SPS prior to administration, with removal of the potassium-rich resin precipitant prior to feeding, hopefully reducing the risk of

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Table 1. Summary of all published studies, in the English language, examining the effects of enteral feed pre-treatment with polystyrene sulfonate

Study	Enteral nutrition	Type of SPS	Dose of SPS (g/mEqK)	Pre-treatment	K change	Na change	Ca change	Mg change	Other change	Other
Palma et al. (USA) [18]	Not specified	SPS	Initially 0.5–1.0 Reduced to 0.3–0.6	Shaken 1 min, fridge 30–60 min	↓ 26% ^a (serum) (31.6% hypok)	↑ 4.1% ^a (serum) (26.3% hyperNa)	↔ (21.1% hypoCa)	↔	↑ P ^a	↔ Bic, Cl
Taylor et al. (USA) [11]	Suplena and Similac PM 60/40	SPS suspension (study also looked at pretreating with Renvela, and combined SPS and renvela)	0.25, 0.5 and 1.0	Shaken 60 s, fridge 30–60 min	Suplena: ↓ 9, 6, 34% (per dose) Similac: ↓ 33 ^a , 42 ^a , 63% (per dose)	Suplena: ↑ 89 ^a , 182 ^a , 260% (per dose) Similac: ↑ 86 ^a , 188 ^a , 247% (per dose)	Suplena: ↓ 11, 17 ^a , 38% (per dose) Similac: ↓ 8, 13, 29% (per dose)	Suplena: ↔ Similac: ↓ 26 ^a , 17, 3% (per dose)	Suplena: ↑ pH ^a ↓ Cu (3, 3, 11%) ↓ Mn (3, 7 ^a , 16%) (0, 2, 7%) ↓ Zn (linear, 5, 10 ^a , 20%) ↑ Fe (linear, 9 ^a , 25 ^a , 34%) ↑ S (19, 45 ^a , 41%) Similac: ↓ Cu (19 ^a , 5, 14%) ↓ Fe (linear, 13, 53 ^a , 87%) ↔ P, S, Zn ↓ 5% Creat ^a	↑ Al (linear)
Thompson et al. (USA) [12]	Expressed breast milk and Similac PM 60/40	SPS (Kayexalate)	0.4–1.5	Shaken 2 min, fridge 60–120 min	↓ 24% ^a (serum) (↓ 18–50% in pre-treated formula)	↑ 2% (serum) (not significant)	↓ 7% ^a	↔	↔	↔ Bic, BUN, Cl, P
Cameron et al. (Canada) [13]	Nestle Good Start	Brand name SPS (Kayexalate) and generic SPS	10, 20, 30 and 40 mL	Shaken 2 min, fridge for 1 h and 24 h	↓ 53–88% No change 1/24 h	↑ 324–494% No change 1/24 h				
Bonmati et al. (Spain) [14]	Osmolite HN, Nutrison Standard, IsoSource Standard	Resinsodio (SPS) and resincalcio (CPS)—numbers not included	15 and 30 g/L	Mixed 15 min, standing 48 h at 37°C	↓ roughly 65–75% (per dose)	↑ 147–191% (per dose) (range 127–215%)	↓ roughly 67–76% (per dose)	↓ roughly 65–72% (per dose)		
Rivard et al. (USA) [15]	Impact 1.5 (high protein)	SPS (Kayexalate)	0.5 or 1.0	Mixed 20 min, stand 24 h	↓ 25–36% (per dose)	↑ 243–342% (per dose)	↓ 13.7–13% (per dose)	↔	Modest ↑ P, Fe, Zn	Modest ↓ in protein
Fassinger et al. (USA) [16]	Similac PM 60/40	SPS and CPS (calcium resonium)	1.0	Mixed 20 min, fridge 50 min	↓ 78% (12% CPS)	↑ 3.85-fold (↓ by CPS)	↔	↔	↔ Zn	
Bunchman et al. (USA) [10]	13 juices, milks and formulas	Granular and sorbitol suspended	1.0	Shaken 1 min, fridge 30 min	↓ 38–81%	↑ 93–527%	↓ 45–84%	↓ 35–100%		
Starbuck (USA) [17]	Milk	Dowex and AG resins	Various number of tablespoons	Stirred, decanted after settling	↓ roughly 80% effect plateaus	↑ roughly 380% effect linear	↓ 35–72%			Slight ↓ pH and protein

CPS, calcium polystyrene sulphonate; ↑, increased; ↓, decreased; ↔, unchanged; K, potassium; Na, sodium; Ca, calcium; Mg, magnesium; Bic, bicarbonate; Cl, chloride; Cu, copper; Fe, iron; Zn, zinc; Mn, manganese; P, phosphorus; S, sulphur; Al, aluminium; BUN, blood urea nitrogen; Creat, creatinine.

^aStatistically significant change if commented on.

the above-mentioned adverse effects while still optimizing nutrition.

Several prior studies confirm that pretreatment of enteral nutrition with SPS lowers the potassium content of feeds significantly [10–17]. Other electrolyte disturbances are also reported, most notably a significant increase in feed sodium content (universal in all studies) [10–17]. In addition, measured levels of calcium, magnesium and phosphate within the feed are all reported to be impacted by pretreatment with SPS, although there is less cross-study agreement on the severity and nature of the change. These studies are summarized in Table 1. Importantly, all of these studies, with the exception of five cases observed by Bunchman et al. [10] and a retrospective cohort study of 13 patients by Thompson et al. [12], were conducted *in vitro*. This is therefore the second retrospective study to describe the clinical consequences of pretreating feeds with SPS *in vivo*, and although it demonstrated a similar electrolyte profile to Thompson et al., had a longer follow-up period [12].

The rates of clinical hypokalaemia (31.6%) and hypernatraemia (26.3%) described by Palma et al. [18] mimic the *in vitro* findings on the potassium and sodium content of feeds following pretreatment with SPS [10–17], although the degree of electrolyte disturbance is less marked. For example, clinical hypernatraemia developed following SPS pretreatment in only five cases (26.3%), despite the reported increase in *in vitro* studies of sodium feed content by 86–527% [10, 11, 13–17]. Most *in vitro* studies also demonstrate a reduction in feed calcium content following pretreatment with SPS (range 8–84%) [10, 11, 14, 15, 17], contributing to the reported incidence of episodic hypocalcaemia seen by Palma et al. [18] in four cases (21.1%). The impact on ionized calcium, a more relevant *in vitro* measurement, remains unknown. The preparation and method of pretreatment of enteral nutrition with SPS had a similar methodology compared with other studies, so does not explain the *in vivo* and *in vitro* differences. Independent of potassium, sodium and calcium, Palma et al. [18] found no significant difference in bicarbonate or chloride levels, which is consistent with the previous *in vivo* study by Thompson et al. [12]. However, as demonstrated in other studies (see Table 1) [11, 15, 16], due to the non-specific binding nature of SPS, there may be significant, yet inconsistent effects on other essential trace elements such as zinc, copper and manganese. Although not as acutely life-threatening as fluctuations in potassium and calcium, these are essential for adequate growth and maintenance of health [19].

Children with CKD are a heterogeneous population, differing in age, size, associated comorbidities, concomitant medications that may be present and, most importantly, aetiology. Congenital anomalies of the kidney and urinary tract are the most common cause of CKD in infants and younger children, while glomerular disorders are a more common aetiology in older children, particularly >12 years of age [2]. The clinical implications of increased sodium content in feed following pretreatment with SPS may be more profound depending on the underlying primary renal disease. For example, children with a salt-wasting nephropathy may be less vulnerable to higher sodium loads than others.

The most informative aspect of this report is the adverse effect profile. Although common practice in some paediatric nephrology units and first described some 45 years ago, the authors correctly identify the paucity of evidence to support the practice of pretreatment and are to be commended for their efforts in compiling this case series to highlight the adverse effect profile, particularly the potentially serious complications

that can arise. They report that 47.4% of patients required a dose adjustment after the first week of treatment and half of courses were discontinued due to adverse effects. Importantly, in 2 of the 14 patients, these effects were potentially life-threatening events. The gastrointestinal disturbances and hypocalcaemia described in the first case are similar to case reports elsewhere: Kakajiwala et al. [20] describe two cases of hypocalcaemia and metabolic alkalosis attributed to the use of SPS, where one child was receiving pretreated formula. In the second case of potentially life-threatening adverse events described by Palma et al. [18], although causation cannot be certain due to other comorbidities, clinicians must be aware that the addition of SPS to feeds is not a benign or risk-free intervention. Furthermore, these events occurred with correct preparation and pretreatment in a hospital environment. The risk profile of continuing SPS pretreatment in the community setting has not been evaluated. Despite this, hyperkalaemia also carries significant risks and any efforts to improve the management of this challenging aspect of CKD are to be lauded.

Palma et al. [18] have described their centre's experience of pretreatment of feeds with SPS, providing a cautionary tale to all paediatric nephrologists—simplifying the administration of a medication through pretreatment is not necessarily beneficial. The adverse effect profile must be considered in all patients prior to commencing pretreatment. Where it is felt to be essential, we heartily agree with the authors' conclusions that close monitoring of electrolytes is mandatory. Much more work is needed to identify those patient cohorts for which this can indeed be considered a safe and effective intervention.

Conflict of interest statement

None declared.

References

1. Rees L, Mak RH. Nutrition and growth in children with chronic kidney disease. *Nat Rev Nephrol* 2011; 7: 615–623
2. Becherucci F, Roperto RM, Materassi M et al. Chronic kidney disease in children. *Clin Kidney J* 2016; 9: 583–591
3. US Food and Drug Administration product information label. https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/011287s023lbl.pdf (18 December 2017, date last accessed)
4. Saginur M, Thiesen A, Lacson A et al. Small intestinal transplant mucosal necrosis associated with enteral sodium polystyrene sulfonate administration. *Am J Transplant* 2012; 12: 3152–3154
5. McGowan CE, Saha S, Chu G et al. Intestinal necrosis due to sodium polystyrene sulfonate (Kayexalate) in sorbital. *South Med J* 2009; 102: 493–497
6. Haupt HM, Hutchins GM. Sodium polystyrene sulfonate pneumonitis. *Arch Intern Med* 1982; 142: 379–381
7. Fenton JJ, Johnson FB, Przygodzki RM et al. Sodium polystyrene sulfonate (Kayexalate) aspiration: histologic appearance and infrared microspectrophotometric analysis of two cases. *Arch Pathol Lab Med* 1996; 120: 967–969
8. Ziessman HA. Alkalosis and seizure due to a cation: exchange resin and magnesium hydroxide. *South Med J* 1976; 69: 497–498
9. Schroder CH, van den Berg AMJ, Willems JL et al. Reduction of potassium in drinks by pre-treatment with calcium polystyrene sulphonate. *Eur J Pediatr* 1993; 152: 263–264

10. Bunchman TE, Wood EG, Schenck MH et al. Pretreatment of formula with sodium polystyrene sulfonate to reduce dietary potassium intake. *Pediatr Nephrol* 1991; 5: 29–32
11. Taylor JM, Oladitan L, Carlson S et al. Renal formulas pretreated with medications alters the nutrient profile. *Pediatr Nephrol* 2015; 30: 1815–1823
12. Thompson K, Flynn J, Okamura D et al. Pretreatment of formula or expressed breast milk with sodium polystyrene sulfonate (Kayexalate) as a treatment for hyperkalemia in infants with acute or chronic renal insufficiency. *J Ren Nutr* 2013; 23: 333–339
13. Cameron JCF, Kennedy D, Feber J et al. Pretreatment of infant formula with sodium polystyrene sulfonate. *Pediatr Drugs* 2013; 15: 43–48
14. Bonmati EM, Bondia FT, Milara J et al. The in vitro effect of the addition of ion exchange resins on the bioavailability of electrolytes in artificial enteral feeding formulas. *Farm Hosp* 2008; 32: 91–95
15. Rivard AL, Raup SM, Beilman GJ. Sodium polystyrene sulfonate used to reduce the potassium content of a high protein enteral formula: a quantitative analysis. *JPEN J Parenter Enteral Nutr* 2004; 28: 76–78
16. Fassinger N, Dabbagh S, Mukhopadhyay S et al. Mineral content of infant formula after treatment with sodium polystyrene sulfonate or calcium polystyrene sulfonate. *Adv Perit Dial* 1998; 14: 274–277
17. Starbuck WC. Reduction of potassium and calcium in milk by sodium sulfonated polystyrene resins. *Kidney Int* 1972; 2: 175–177
18. Palma KL, Pavlick ER, Copelovitch L. Pretreatment of enteral nutrition with sodium polystyrene sulfonate: effective, but beware the high prevalence of electrolyte derangements in clinical practice. *Clin Kidney J* 2018; 11: 166–171
19. Filler G, Felder S. Trace elements in dialysis. *Pediatr Nephrol* 2014; 29: 1329–1335
20. Kakajiwala A, Barton KT, Rampolla E et al. Acute hypocalcemia and metabolic alkalosis in children on cation-exchange resin therapy. *Case Rep Nephrol* 2017; 2017: 6582613