Sodium polystyrene sulfonate: still news after 60 years on the market

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Issue Section: Editorial

Hyperkalaemia is common and potentially life-threatening in multiple clinical settings, especially in chronic kidney disease (CKD) [1, 2]. Potassium-binding resins (K resins) have been used for 60 years for the treatment of hyperkalaemia [3]. Sodium polystyrene sulfonate (SPS) is a cross-linked polymer whose reactive sulfonic groups exchange preloaded sodium (Na) for another cation. As a result of the concentrations of Na^+ and K^+ along the gastrointestinal (GI) lumen, the single favourable site for Na^+–K^+ exchange is the colon [4]. Although the exchanging capacity of SPS is 1 mEq of potassium per 1 g of resin, efficiency *in vivo* is lower because sodium release is only partial. Thus only ~10 mEq of potassium will be bound and excreted per 30 g of SPS [5]. SPS was approved by the US Food and Drug Administration (FDA) in June 1958 as a 'short-term' treatment for hyperkalaemia, at a time when dialysis was in its infancy [6], and 4 years before drug manufacturers were required to prove the effectiveness and safety of their products to market them. In 1962, on the basis of a moderate potassium reduction (−0.9 ± 0.1 mEq/L within 24 h, $P < 0.0001$) observed in a small uncontrolled study [$n = 32$ hyperkalaemic patients receiving oral ($n = 24$) or rectal ($n = 8$) SPS in water, intravenous 20% dextrose and low-potassium diet] [3], the FDA's Drug Efficacy Study Implementation Program considered SPS (Kayexalate powder) as 'effective'. Of note, SPS was not administered with a cathartic in this study, but in water [3]. Given that the reduction of potassium levels is delayed for at least 2 h and peaks at 4–6 h, SPS is not indicated as an emergency intervention for hyperkalaemia [7, 8]. Although not available in the USA, calcium polystyrene sulfonate (CaPS), which entraps

potassium in exchange for calcium, is also used in many other countries [9].

Despite their long-term and common use in some countries, data on the efficacy of K resins to reduce K levels are limited to a few uncontrolled studies and small trials, with ambiguous and even conflicting results until very recently. A small (n = 33 CKD patients with mild hyperkalaemia) randomized placebo-controlled trial (RCT) showed a significant decrease of potassium levels (~1 mEq/L) after a 7-day treatment with SPS compared with placebo [10], whereas a recent retrospective cohort (n = 122 patients, 38% with CKD) documented a direct relationship between SPS dose (15, 30, 45 and 60 g) and a reduction in K levels after a single dose (from −0.82 ± 0.48 to −1.4 ± 0.42 mmol/L, respectively) [11]. Furthermore, the K level reached the normal range in 94% of patients after SPS. Overall, the wide variability in the use of K resins between haemodialysis units and countries participating in the Dialysis Outcomes and Practice Pattern Study (DOPPS) may reflect, at least partially, the uncertainty concerning their actual efficacy [9].

In contrast to the paucity of literature regarding the efficacy of K resins, severe constipation was recognized as an adverse effect of SPS very shortly after FDA approval [3]. Therefore a suspension of SPS in 70% sorbitol was approved in 1982 for use in the USA [12]. Since then, serious and sometimes fatal GI injury, mainly colonic necrosis, has repeatedly been attributed to the use of both oral [13] and especially rectal [14] SPS–sorbitol co-administration. After an initial request to reformulate the resin with 33% instead of 70% sorbitol [3], in 2009 the FDA issued a black box warning against the concomitant formulation of SPS and 70% sorbitol in high-risk patients, including those with a history of bowel disease or surgery [6]. Nonetheless, a systematic review of case reports documented that in 17 of 58 cases of biopsy-proven GI injury associated with SPS (1948–2011), the SPS preparation did not contain sorbitol [15], showing that GI adverse events may occur with SPS alone. GI injury was not limited to the colon (44/58 patients) but was also observed in the small intestine (n = 12) and in the upper GI tract (n = 2), as previously reported [16]. Of note, several cases of colonic necrosis have also been reported under CaPS use, with daily doses ranging from 45 to 90 g, with or without sorbitol [17].

Over the past decades, the available information was limited to case reports and case series, leading to persistent ambiguity regarding the strength of the association. The first estimate of risk was provided by a retrospective case–control study including 123 391 inpatients (2194 being prescribed SPS, almost all receiving oral SPS in 33% sorbitol) at a tertiary hospital over a 9-year period [18]. Although this study showed a 2-fold (non-significant) increase in the incidence of colonic necrosis in SPS users compared with non-users, SPS-associated colonic necrosis was extremely rare (0.14% versus 0.07%, respectively; relative risk 2.1, P = 0.2). Indeed, among 82 tissue-confirmed cases of colonic necrosis, only 3 were associated with SPS use (occurring within 30 days after SPS prescription, regardless of whether SPS crystals were present). Of note, none of the 850 outpatients prescribed SPS presented colonic necrosis. Although this study undoubtedly represented definite progress, the risk of GI injury is likely to have been underestimated because only cases of biopsy-proven colonic necrosis were included. SPS was not associated with GI adverse events compared with placebo in the RCT by Lepage *et al.* [10], but the duration of treatment was short (6.9 days). Importantly, no severe GI adverse event was documented in a recent retrospective study from South Korea, including 247 patients with CKD (eGFR 30 ± 15 mL/min/1.73 m^2) and mild hyperkalaemia, using low doses of CaPS (8 g/day) for up to 56 months [17].

In this issue of *Nephrology Dialysis Transplantation*, Laureati *et al.* [19] publish data based on the Swedish Renal Registry and the Swedish national drug dispensation register. They examined SPS use and GI safety during 2006–16. Among 19 530 adults (mean age 73 years) with CKD Stages 4–5 (2714 on chronic dialysis), naive to SPS, 3690 initiated oral SPS without sorbitol (1288 on chronic dialysis), with 60% for chronic use and using lower dosages in 85% of cases than recommended by the product label. Compared with unexposed periods and after adjustment for 26 covariates, SPS use was associated with hospitalization or death due to intestinal ischaemia/thrombosis or GI ulcers and perforation {hazard ratio [HR] 1.25 [95% confidence interval (CI) 1.05–1.49]}. The risk was higher in patients treated with the recommended ‘per label’ (high) dose. When each GI outcome was considered separately, the association persisted for GI ulceration and perforation but was not significant for intestinal ischaemia

or thrombosis, possibly due to the low number of events. Furthermore, the risk for minor GI adverse events (requiring *de novo* prescription of laxatives or anti-diarrheal drugs) was also higher during SPS exposure [HR 1.11 (95% CI 1.03–1.19)], with again a stronger association for higher ('per label') doses. Of note, the association of both severe and minor GI events could not be demonstrated for low SPS dosages. Surprisingly, this is the first study providing detailed practice patterns of SPS use (prescription and dispensation) in a nation-wide cohort, 60 years after the start of clinical use [19]. A definite strength of the study is the contemporary pattern of use.

Interestingly, SPS is dispensed chronically in more than half of Swedish CKD Stage G4-5 patients, at moderate to low dosages, which means that in most cases it is prescribed 'off label' for chronic K control. This is in line with the K resin prescription patterns documented in the DOPPS. Indeed, when prescribed in HD patients, K resins are used for the chronic prevention or management of hyperkalaemia, as suggested by the dose and frequency of the prescription (from 15 g daily to 15 g weekly) [9]. Interestingly, a large recent retrospective population-based cohort study from Canada including 40 040 older adults (≥66 years) similarly documented a significant 2-fold higher incidence of hospitalization for serious adverse GI events in 20 020 SPS users within 30 days of first prescription compared with 20 020 matched non-users [20]. Although GI serious injury remained a rare event [37 events in users (0.2%) versus 18 events in non-users (0.1%)], the increased risk was consistent in high-risk subpopulations and after several sensitivity analyses. However, characteristics of the included population (mean age 78 years, diabetes 52%, numerous comorbidities) make it difficult to extrapolate the results to younger, less ill individuals. Additionally, the actual dose and route of SPS administration were not known and the number of events was small in some subgroups. Of note, only 1% of included patients were on maintenance dialysis [20].

Where do we go from here? Should SPS use be definitively discouraged? Although these new findings document some concern about SPS GI safety, they deserve several comments. First, as previously documented [15], the increased incidence of both severe and minor GI events among SPS users appears to be

dose-dependent, with no clear association in low-dose users. Indeed, 'high' doses in this study were 'per label' doses, i.e. those recommended by the FDA for 'short-term' treatment of hyperkalaemia (15 g two to four times per day until normalization of potassium levels) [5]. Second, as acknowledged by Laureati *et al*. [19], this observational study does not prove causality because GI injury could also be favoured by conditions concomitantly causing hyperkalaemia and GI harm, especially in patients with advanced CKD and comorbidities. Third, although relative risks for GI events are increased, absolute risks remain very low. Finally, as in the Canadian cohort [20], patients participating in this study were older (mean age 73 years) and suffered from many comorbidities. Admittedly, these characteristics are found in most CKD patients. However, the risk of GI adverse events may be lower in younger patients, even with CKD.

Patiromer, an organic polymer exchanging potassium for calcium in the distal colon, has been approved by the FDA and European Medicines Agency (EMA) in 2015 and 2017, respectively, for the treatment of hyperkalaemia, on the basis of significant, dose-dependent reductions in serum potassium at 48 h and ability to maintain normokalaemia over months of therapy in most CKD patients with mild to moderate hyperkalaemia [21–23]. Unfortunately, none of the above-mentioned trials included patients with Stage 5 CKD. The safety profile of patiromer was considered to be acceptable. Constipation, the most common side effect (11% of patients), required patiromer withdrawal in very few patients. There were no serious GI adverse events. Hypomagnesaemia was observed in 5.9% of patients on patiromer versus no patient receiving placebo [21, 23].

Sodium zirconium cyclosilicate (ZS-9 or SZC) is a highly selective inorganic crystalline cation exchanger that entraps potassium in exchange for hydrogen and sodium in the GI lumen, showing >25-fold selectivity for K^+ over either Ca^{2+} or Mg^{2+} [24]. The onset of effect is within 1 h [25], and SZC was effective in lowering moderate to severe hyperkalaemia within 4 h in two Phase III clinical trials [25, 26]. Furthermore, SZC was effective at lowering potassium, even in CKD Stage 5 [27] and chronic HD patients [28]. These findings led to approval for the treatment of hyperkalaemia by both the FDA and EMA in 2018. In a Phase III clinical trial including 753 patients with mild to moderate

hyperkalaemia (593 and 158 receiving increasing doses of SZC and placebo, respectively), diarrhoea was the most common side effect in both groups, although not frequently observed (1.8% and 2.5% in the ZS-9 and placebo groups, respectively) [25]. A dose-dependent mild increase in serum bicarbonate (probably due to ammonium-ion trapping) [29] was also detected, a finding that can hardly be considered as a concern or side effect in late CKD or dialysis patients prone to metabolic acidosis, as was a prolongation of the corrected QT interval (from 0.03 to 10.3 ms) [25]. Hypomagnesaemia was not observed. Of note, oedema occurred in 13.1% of 61 SZC patients with heart failure in the Hyperkalemia Randomized Intervention Multidose ZS-9 Maintenance (HARMONIZE) trial, a higher frequency than in the placebo group, and a role for the sodium content of SZC cannot be excluded [30]. Interestingly in the very recent Dialyze study in HD patients, interdialytic weight gain, usually tightly correlated with salt balance, was not significantly different in patients randomized to SZC versus placebo, a reassuring finding.

In conclusion, the study by Laureati *et al.* [19] expands on previous evidence of GI adverse events associated with SPS use. However, GI events remain rare and dose-dependent. The increased risk of GI adverse outcomes is documented for higher dosages, recommended only for the short-term treatment of hyperkalaemia. The long-term experience with SPS use and the large number of patients treated with SPS in many countries should be balanced with the much greater quality of scientific data available for the new K binders. However, although patiromer and SZC undoubtedly progress the treatment of hyperkalaemia, relatively recent real-life experience with both new molecules suggests that their tolerance is better than that of SPS, but unfortunately there have been no head-to-head comparisons between SPS and any of the new, more expensive binders. More data are required about the long-term safety and tolerance of the latter, especially in patients with severe/end-stage CKD. On the basis of current evidence, SPS should be avoided at high doses for continuous use, especially in patients with bowel disease or recent GI surgery. In contrast, we still use this molecule for chronic hyperkalaemia, but at lower dosages and off label, awaiting hopefully the widespread reimbursement in ESKD patients of the newer K binders.

CONFLICT OF INTEREST STATEMENT

Dr. Labriola reports personal fees from Amgen, personal fees from Sanofi, personal fees from Vifor Fresenius Medical Care Renal Pharma, outside the submitted work. Dr. Jadoul reports personal fees from Vifor Fresenius Medical Care Renal Pharma, personal fees from Astra-Zeneca, outside the submitted work.

REFERENCES

1 Einhorn LM, Zhan M, Hsu VD et al. The frequency of hyperkalemia and its significance in chronic kidney disease. *Arch Intern Med* 2009; 169: 1156–1162

Google Scholar Crossref PubMed

2 Kovesdy CP. Management of hyperkalemia: an update for the internist. *Am J Med* 2015; 128: 1281–1287

Google Scholar Crossref PubMed

3 Scherr L, Ogden DA, Mead AW et al. Management of hyperkalemia with a cation-exchanging resin. *N Engl J Med* 1961; 264: 115–119

Google Scholar Crossref PubMed

4 Johnson LR. Fluid and electrolyte absorption. In: *Gastrointestinal Physiology*, 5th edn. Philadelphia: Mosby Yearbook 1997: 135–145

Google Scholar

5 US Food and Drug Administration. *Kayexalate®: Sodium polystyrene sulfonate, USP, Cation-exchanging resin*. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/011287s022lbl.pdf (5 September 2019, date last accessed)

6

Watson M, Abbott KC, Yuan CM. Damned if you do, damned if you don't: potassium binding resins in hyperkalemia. *Clin J Am Soc Nephrol* 2010; 5: 1723–1726

Google Scholar Crossref PubMed

7 Kamel KS, Schreiber M. Asking the question again: are cation exchange resins effective for the treatment of hyperkalemia? *Nephrol Dial Transplant* 2012; 27: 4294–4297

Google Scholar Crossref PubMed

8 Sterns RH, Rojas M, Bernstein P et al. Ion-exchange resins for the treatment of hyperkalemia: are they safe and effective? *J Am Soc Nephrol* 2010; 21: 733–735

Google Scholar Crossref PubMed

9 Jadoul M, Karaboyas A, Goodkin DA et al. Associations with serum chemistries and interdialytic weight gain in hemodialysis patients. *Am J Nephrol* 2014; 39: 252–259

Google Scholar Crossref PubMed

10 Lepage L, Dufour AC, Doiron J et al. Randomized clinical trial of sodium polystyrene sulfonate for the treatment of mild hyperkalemia in CKD. *Clin J Am Soc Nephrol* 2015; 10: 2136–2142

Google Scholar Crossref PubMed

11 Kessler C, Ng J, Valdez K et al. The use of sodium polystyrene sulfonate in the inpatient management of hyperkalemia. *J Hosp Med* 2011; 6: 136–140

Google Scholar Crossref PubMed

12 Flinn RB, Merrill JP, Welzant WR. Treatment of the oliguric patient with a new sodium-exchange resin and sorbitol; a preliminary report. *N Engl J Med* 1961; 264: 111–115

Google Scholar Crossref PubMed

13 Gerstman BB, Kirkman R, Platt R. Intestinal necrosis associated with postoperative orally administered sodium polystyrene sulfonate in sorbitol. *Am J Kidney Dis* 1992; 20: 159–161

Google Scholar Crossref PubMed

14 Lillemoe KD, Romolo JL, Hamilton SR et al. Intestinal necrosis due to sodium polystyrene sulfonate (Kayexalate) in sorbitol enemas: clinical and experimental support for the hypothesis. *Surgery* 1987; 101: 267–272

Google Scholar PubMed

15 Harel Z, Harel S, Shah PS et al. Gastrointestinal adverse events with sodium polystyrene sulfonate (Kayexalate) use: a systematic review. *Am J Med* 2013; 126: 264.e9-24

Google Scholar Crossref

16 Abraham SC, Bhagavan BS, Lee LA et al. Upper gastrointestinal tract injury in patients receiving Kayexalate (sodium polystyrene sulfonate) in sorbitol: clinical, endoscopic and histopathologic findings. *Am J Surg Pathol* 2001; 25: 637–644

Google Scholar Crossref PubMed

17 Yu MY, Yeo JH, Park JS et al. Long-term efficacy of oral calcium polystyrene sulfonate for hyperkalemia in CKD patients. *PLoS One* 2017; 12: e0173542

Google Scholar Crossref PubMed

18 Watson MA, Baker TP, Nguyen A et al. Association of prescription of oral sodium polystyrene sulfonate with sorbitol in an inpatient setting with colonic necrosis: a retrospective cohort study. *Am J Kidney Dis* 2012; 60: 409–441

Google Scholar Crossref PubMed

19 Laureati P, Trevisan M, Schallin L et al. Initiation of sodium polystyrene sulfonate and the risk of gastrointestinal adverse events in advanced CKD: a nationwide study. *Nephrol Dial Transplant* 2019. doi: 10.1093/ndt/gfz150

20 Noel JA, Bota SE, Petrcich W et al. Risk of hospitalizations for serious adverse gastrointestinal events associated with sodium polystyrene sulfonate use in patients with advanced age. *JAMA Intern Med* 2019; 179: 1025

Google Scholar Crossref

21 Pitt B, Anker SD, Bushinsky DA et al. , PEARL-HF Investigators. 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 (PEARL-HF trial). *Eur Heart J* 2011; 32: 820–828

Google Scholar Crossref PubMed

22 Bakris GL, Pitt B, Weir MR et al. Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease: the AMETHYST-DN randomized clinical trial. *JAMA* 2015; 314: 151–161

Google Scholar Crossref PubMed

23 Weir MR, Bakris GL, Bushinsky DA et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med* 2015; 372: 211–221

Google Scholar Crossref PubMed

24 Stavros F, Yang A, Leon A et al. Characterization of structure and function of ZS-9, a K^+ selective ion trap. *PLoS One* 2014; 9: e114686

Google Scholar Crossref PubMed

25 Packham DK, Rasmussen HS, Lavin PT et al. Sodium zirconium cyclosilicate in hyperkalemia. *N Engl J Med* 2015; 372: 222–231

Google Scholar Crossref PubMed

26 Kosiborod M, Rasmussen HS, Lavin PT et al. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. *JAMA* 2014; 312: 2223–2233

Google Scholar Crossref PubMed

27 Roger SD, Lavin PT, Lerma EV et al. Long-term safety and efficacy of sodium zirconium cyclosilicate for hyperkalemia in patients with mild/moderate versus severe/end-stage chronic kidney disease: comparative results from an open-label, phase 3 study. *Nephrol Dial Transplant* 2019. doi: 10.1093/ndt/gfz285

28 Fishbane S, Ford M, Fukagawa M et al. A phase 3b, randomized, double-blind, placebo-controlled study of sodium zirconium cyclosilicate for reducing the incidence of predialysis hyperkalemia. *J Am Soc Nephrol* 2019; 30: 1723–1733

Google Scholar Crossref PubMed

29 Beccari MV, Meaney CJ. Clinical utility of patiromer, sodium zirconium cyclosylicate, and sodium polystyrene sulfonate for the treatment of hyperkalemia: an evidence-based review. *Core Evid* 2017; 12: 11–24

Google Scholar Crossref PubMed

30 Anker SD, Kosiborod M, Zannad F et al. Maintenance of serum potassium with sodium zirconium cyclosilicate (ZS-9) in heart failure patients: results from a phase 3 randomized double-

blind, placebo-controlled trial. *Eur J Heart Fail* 2015; 17: 1050–1056

Google Scholar Crossref PubMed

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