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**Nephrol Dial Transplant (2012): Editorial Comment**

**Asking the question again: are cation exchange resins effective for the treatment of hyperkalemia?**

Kamel S. Kamel1,2 and Martin Schreiber2

1Division of Nephrology, Keenan Research Centre in the Li Ka Shing Knowledge Institute of St Michael’s Hospital, Toronto, Ontario, Canada and 2Division of Nephrology, University of Toronto, Toronto, Canada

**Correspondence and offprint requests to:** Kamel S. Kamel; E-mail: Kamel.kamel@utoronto.ca

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Sodium polystyrene sulfonate (Kayexalate®) is a cross-linked polymer to which reactive sulfonic groups are attached and preloaded with sodium (Na+). When placed in a solution, its reactive sulfonate groups exchange their bound Na+ for another cation in the solution. Sodium polystyrene sulfonate (SPS) [Although ‘SPS’ is often used as an abbreviation for sodium polystyrene sulfonate, SPS® is actually a brand name for sodium polystyrene sulfonate in sorbitol.] has long been used for the treatment of hyperkalemia, assuming that its reactive sulfonate groups exchange bound Na+ for potassium (K+) in the lumen of the gastrointestinal (GI) tract, causing loss of K+ in stool.

Because it tends to cause constipation, SPS is usually given with sorbitol as a cathartic. In September 2009, the US Food and Drug Administration recommended against the ‘concomitant use of sorbitol’ with Kayexalate® powder because of concerns about the risk of colonic necrosis and other serious GI side effects (bleeding, ischemic colitis and perforation). This warning, however, did not apply to premixed SPS in 33% sorbitol. A debate followed on the issue of use of cation-exchange resins in the treatment of hyperkalemia; sodium polystyrene sulfonate (SPS®) is actually a brand name for sodium polystyrene sulfonate in sorbitol. A debate followed on the issue of use of cation-exchange resins in the treatment of hyperkalemia; sodium polystyrene sulfonate (SPS®) is actually a brand name for sodium polystyrene sulfonate in sorbitol.
hyperkalemia [1, 2]. In a previous editorial, Kamel and Wei [3] discussed the issue of the use of cation-exchange resins in the treatment of hyperkalemia. In this editorial, we ask the question again: are cation exchange resins effective in treatment of hyperkalemia? Our analysis is based on considerations of the binding characteristics of SPS, the concentration of electrolytes in the lumen of different segments of the GI tract, what is required to achieve a high rate of excretion of K⁺ in stool, and on examining the available evidence in the literature.

SPS contains 4 mEq of Na⁺ per gram, which could be available for exchange for K⁺ in the lumen of the GI tract. Emmett et al. [4] examined the binding of K⁺ to SPS in vitro by mixing the resin with solutions with a varied concentration of potassium chloride. At [K⁺] of 100 mmol/L, only 2 mmol of Na⁺ was exchanged for K⁺ per gram of resin. As Na⁺ was released and its concentration in the solution rose (65 mmol/L), the exchange of Na⁺ for K⁺ became limited. Considering the concentrations of Na⁺ and K⁺ at different sites in the lumen of the GI tract, the only favorable site for this exchange is likely in the lumen of the rectum (or perhaps the entire colon) where the concentration of Na⁺ is ~10 mmol/L and the concentration of K⁺ is ~80 mmol/L [5]. Notwithstanding other cations such as NH₄⁺ [whose concentration in stool may be high in patients with end-stage renal disease (ESRD)], Ca²⁺ and Mg²⁺ will compete with K⁺ for this exchange with Na⁺. Furthermore, even if the exchange of Na⁺ for K⁺ was to occur in the colon, there is only a small amount of K⁺ to bind the resin. The amount of K⁺ excreted via the GI tract in normal subjects is ~90 mmol/day [6, 7]. Although it has been suggested that patients with ESRD have an enhanced colonic excretion of K⁺, the bulk of evidence from balance studies suggests that ESRD patients may excrete only a few extra millimoles of K⁺ daily in their stool [8].

A theoretical benefit to the use of resins is if they were to bind K⁺ and lower its concentration in luminal water, this may enhance K⁺ secretion by the recto-sigmoid colon. The issue, however, is how to achieve a large loss of K⁺ from the GI tract over a relatively short period of time, as would be required in a patient who presents with moderately severe hyperkalemia in whom the decision is made not to start dialysis but to induce K⁺ loss in stool instead. The limiting factor for a large K⁺ loss via the GI tract is stool volume. In quantitative terms, if one assumes a transepithelial lumen negative voltage in the colon even as high as ~80 mV (measured values in patients with ESRD are close to ~45 mV [9]) and a plasma [K⁺] (P_K) of 5 mmol/L, the [K⁺] in stool water would be 100 mmol/L. With the usual stool weight of 125 g/day, of which 75% is water (i.e. 100 mL), the rate of excretion of K⁺ would be 10 mmol/day. Inducing diarrhea is required to achieve a large loss of K⁺ from the GI tract over a relatively short period of time. TEV, transepithelial voltage.

administration of cathartics? As shown by Emmett et al. [4], after administration of 60 g of sorbitol, an osmotic cathartic, to normal subjects, the mean stool weight was 788 g over 12 h and the total K⁺ output was 26 ± 2 mmol over that time period. The addition of resin did not add much in terms of K⁺ loss, as the total K⁺ output was 30 ± 6 mmol. While only 30% of the administered resin was recovered in stool over that time period, it remains that over a short period of time, the leverage to induce an appreciable loss of K⁺ via the GI tract is the induction of a large volume of diarrhea. In this study [4], the largest loss of K⁺ occurred with the administration of phenolphthalein which induces secretory diarrhea and the secretion of K⁺ in the colon. The mean stool weight was 1340 g over 12 h and the total K⁺ loss was 37 ± 4 mmol. When resin was added, 70% of the administered resin was recovered in stools, and total K⁺ output rose to 49 ± 6 mmol.

Two studies are commonly cited to support the use of SPS in the treatment of hyperkalemia. In the study by Flinn et al. [12], SPS was given four times per day and the results for the P_K were reported on Day 5. Of note, patients were given a sufficient amount of sorbitol to produce ‘satisfactory’ diarrhea. Although the number of patients was small, one group of patients who were treated with sorbitol only had an average reduction by Day 5 in P_K that was larger than patients treated with both resin and sorbitol.

Scherr et al. [13] treated 30 patients with hyperkalemia and oliguria with SPS, which was given by mouth in 22 patients and as enema in 8 patients. The dose and duration of treatment varied but most of the patients did not require laxatives as constipation occurred only occasionally. There was no control group. The mean fall in the P_K in the group that received SPS orally was 0.9 ± 0.1 mmol/L in the first 24 h. K⁺ excretion in stool was not measured, so there is no evidence that the administration of resin caused the fecal loss of K⁺ sufficient to account for the fall in P_K. While in 9 of the 30 patients, the fall in P_K was ≤0.4 mmol/L, some patients had impressive falls in P_K in the first 24 h (Table 1). These results are difficult to

![Fig. 1. Stool volume limits the rate of excretion of K⁺ via the GI tract. The cylinder represents the colon. Assuming a transepithelial lumen negative voltage of 80 mV and a P_K of 5 mmol/L, according to the Nernst equation, the concentration of K⁺ in the lumen of the colon will be 100 mmol/L. With a usual stool weight of 125 g/day, of which 75% is water (i.e. 100 mL), the rate of excretion of K⁺ would be 10 mmol/day. Inducing diarrhea is required to achieve a large loss of K⁺ from the GI tract over a relatively short period of time. TEV, transepithelial voltage.](https://academic.oup.com/ndt/article-abstract/27/12/4294/1821589)
or in critically ill patients given resin enema [1, 15]. Re-in the postoperative period (e.g. post-renal transplantation) frequently fatal. Most cases were reported initially in patients which SPS in sorbitol is used, intestinal necrosis is fre-

rather low considering the very high frequency with this complication is not exactly known and is likely to be

involves the ileum and the colon. While the incidence of is the development of intestinal necrosis, which usually

be detected in human pathological specimens, adherent to the injured mucosa [16]. There is also concern that at least some of the recent reports of colonic necrosis followed the use of premixed preparation containing 33% sorbitol [1].

In patients with life-threatening hyperkalemia, there is no role for the use of resins [18], or attempting to induce K⁺ loss via the GI tract with inducing diarrhea as this will require several hours to achieve its effect. In a patient with moderately severe hyperkalemia in whom the decision is made to not start dialysis but to induce K⁺ loss in stool instead, the goal of therapy should be to induce diarrhea. Since there is concern about the use of sorbitol 33%, the role of other cathartics particularly those that induce secretory diarrhea, e.g. bisacodyl, needs to be explored. These diphenolic laxatives, by increasing cyclic adenosine monophosphate in colonic mucosal cells, may not only increase stool volume but also, as suggested by Sandle and Hunter [19], stimulate K⁺ secretion via big conductance K⁺ channels. Addition of SPS to cathartics which induce secretory diarrhea may increase the rate of excretion of K⁺, however the effect is modest compared to that of inducing diarrhea.

What about patients with mild-to-moderate chronic hyperkalemia due, for example, to the use of renin-

angiotensin-aldosterone system (RAAS) blockers or patients with chronic kidney disease who do not yet require dialysis but need to have control of hyperkalemia? There are no studies that have examined the
eefficacy, safety and tolerability of the long-term use of SPS. Furthermore, inducing a state of chronic diarrhea may not be possible or acceptable. In a recent double-blind placebo-controlled trial, Pitt et al. [20] examined the safety and efficacy of RLY5016, a polymeric potassium binder, on Pₖ in heart failure patients receiving spironolactone. Patients were eligible if they had either a history of hyperkalemia resulting in the discontinuation of RAAS blocker or a beta-adrenergic blocking agent or a glomerular filtration rate (GFR) <60 mL/min. The duration of the study was 4 weeks. The baseline Pₖ in both groups was ~4.7 mmol/L. There was a drop in Pₖ in the RLY5061 group by 0.22 mmol/L, whereas Pₖ rose in the placebo group by 0.23 mmol/L. The incidence of hyperkalemia (Pₖ > 5.5 mmol/L) was significantly lower in the RLY5061 group (7%) compared with placebo (25%). Patients randomized to RLY5061 had significantly more GI adverse effects (21%) compared with those randomized to placebo (6%). Of note, none of the patients had hyperkalemia at the start of the study. Therefore, it did not address the issue of whether RLY5061 would be effective in appreciably lowering Pₖ in patients who develop hyperkalemia on RAAS blockers and, therefore, permit the continued use of these drugs. The mean estimated GFR in the treatment group was 84 mL/min. While 6% of the patients in the RLY5061 group developed hypokalemia, the mean drop in Pₖ in the whole group was modest. Within the short duration of the study, almost a quarter of the patients had GI side effects. It remains to be seen whether in fact this new agent will prove to be of long-term benefit in preventing this important and common complication in this group of patients.

In patients with chronic hyperkalemia, decreasing K⁺ intake and the use of diuretics to increase flow in the terminal distal cortical nephron (CCD) seems to be an effective strategy. The point to emphasize (as was illustrated in a quantitative analysis in a recent publication by Kamel and Halperin [21]) is that patients who have disorders and/or are taking drugs that significantly affect the ability to generate transepithelial lumen negative voltage in their CCD are dependent on maintaining a high flow rate in their terminal CCD to maintain K⁺ balance without the need for a higher Pₖ. In the presence of vasopression action, the number of osmoles in its luminal fluid determines the flow rate in the terminal CCD. Owing to the process of intrarenal recycling of urea, a large fraction of the osmoles delivered to CCD are urea osmoles. Therefore, restricting protein intake may decrease the amount of urea recycling and hence the volume of fluid that exits the terminal CCD, and thus diminish the rate of excretion of K⁺. The other major osmoles in the lumen of terminal CCD are Na⁺ and Cl⁻. If the patient is given a diuretic and becomes intravascular volume-depleted, the increase in NaCl reabsorption in the proximal convoluted tubule will decrease the number of osmoles of Na⁺ and Cl⁻ in the lumen of the terminal CCD, and hence the rate of flow in the terminal CCD. Therefore, if diuretics are used to increase the rate of K⁺ excretion, one must be careful to avoid intravascular volume depletion. It has been suggested that an increased delivery of HCO₃⁻ and/or a

### Table 1. Fall in plasma [K⁺] in a subset of patients reported by Scherr et al. [13]

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Dose of resin (g)</th>
<th>Route</th>
<th>Fall in $P_K$ (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>40</td>
<td>p.o.</td>
<td>2.8</td>
</tr>
<tr>
<td>9</td>
<td>40</td>
<td>p.o.</td>
<td>1.7</td>
</tr>
<tr>
<td>27</td>
<td>10</td>
<td>Enema</td>
<td>1.6</td>
</tr>
<tr>
<td>28</td>
<td>30</td>
<td>Enema</td>
<td>2.1</td>
</tr>
</tbody>
</table>

An increasing concern with the use of SPS in sorbitol is the development of intestinal necrosis, which usually involves the ileum and the colon. While the incidence of this complication is not exactly known and is likely to be rather low considering the very high frequency with which SPS in sorbitol is used, intestinal necrosis is frequently fatal. Most cases were reported initially in patients in the postoperative period (e.g. post-renal transplantation) or in critically ill patients given resin enema [1, 15]. Recently, however, McGowan et al. [16] reported 11 cases of intestinal necrosis over a period of 9 years that were temporally related to the use of SPS in sorbitol, 4 of which were fatal. All patients received oral SPS, only two of them were postoperative and only four had ESRD. The harm has generally been attributed to the use of 70% sorbitol, because similar bowel lesions are induced in rats with or without uremia by administering enemas of 70% sorbitol with or without SPS, but not by giving SPS alone [17]. There does seem to be some concern, however, that the resin itself may be involved as SPS crystals can often be detected in human pathological specimens, adherent to the injured mucosa [16]. There is also concern that at least some of the recent reports of colonic necrosis followed the use of premixed preparation containing 33% sorbitol [1].

What about patients with mild-to-moderate chronic hyperkalemia? There are no studies that have examined the

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rise in the pH of luminal fluid in CCD may provide a signal to augment the secretion of \( K^+ \) \[22, 23\]. The role of induction of bicarbonaturia with the use of acetazolamide needs to be examined.

In conclusion, our recommendations for the role of inducing the loss of \( K^+ \) via the GI tract and the use of resins in the treatment of hyperkalemia are summarized in Table 2. We emphasize that these recommendations represent our opinions based on the above analysis and the available published evidence in the literature and remain open to debate.

**Conflict of interest statement.** None declared.

**References**

19. Sandle GI, Hunter M. Apical potassium (BK) channels and enhanced potassium secretion in human colon. *QJM* 2010; 103: 85–89.

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**Table 2. Role of inducing \( K^+ \) loss via the GI tract in the management of hyperkalemia**

<table>
<thead>
<tr>
<th>Setting</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperkalemia with severe ECG changes (e.g. absent P waves, wide QRS complex)</td>
<td>No role for inducing ( K^+ ) loss via GI tract</td>
</tr>
<tr>
<td>Moderately severe hyperkalemia with no or mild ECG changes (e.g. peaked T waves)</td>
<td>Inducing a large loss of ( K^+ ) via GI tract over a short period of time requires a large stool volume</td>
</tr>
<tr>
<td>Diphenolic laxatives which induce secretory diarrhea (e.g. bisacodyl) are likely more effective Addition of SPS to cathartics which induce secretory diarrhea may increase the excretion of ( K^+ )</td>
<td></td>
</tr>
<tr>
<td>Chronic mild–moderate hyperkalemia (outpatient)</td>
<td>No evidence for efficacy or safety of long-term SPS use</td>
</tr>
<tr>
<td>Inducing a chronic state of diarrheal may not be practical, but may be achieved with osmotic laxatives, e.g. lactulose. Avoid the use of sorbitol</td>
<td></td>
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<tr>
<td>Addition of SPS to osmotic cathartics seems to add little in terms of increasing the excretion of ( K^+ )</td>
<td></td>
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<tr>
<td>Role of other ( K^+ ) binders, e.g. RLY5016, is at present uncertain</td>
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