CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Gastrointestinal Adverse Events with Sodium Polystyrene Sulfonate (Kayexalate) Use: A Systematic Review

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ABSTRACT

BACKGROUND: Sodium polystyrene sulfonate (Kayexalate; Sanofi-Aventis, Paris, France) is a cation-exchange resin routinely used in the management of hyperkalemia. However, its use has been associated with colonic necrosis and other fatal gastrointestinal adverse events. Although the addition of sorbitol to sodium polystyrene sulfonate preparations was previously believed to be the cause of gastrointestinal injury, recent reports have suggested that sodium polystyrene sulfonate itself may be toxic. Our objective was to systematically review case reports of adverse gastrointestinal events associated with sodium polystyrene sulfonate use.

METHODS: MEDLINE (1948 to July 2011), EMBASE (1980 to July 2011), Cochrane Central Register of Controlled Trials (CENTRAL) (1993 to July 27, 2011), bibliographies of identified articles, and websites of relevant drug agencies and professional associations in the United States and Canada were reviewed to identify eligible reports of adverse gastrointestinal events associated with sodium polystyrene sulfonate use. Causality criteria of the World Health Organization causality assessment system were applied to each report.

RESULTS: Thirty reports describing 58 cases (41 preparations containing sorbitol and 17 preparations without sorbitol) of adverse events were identified. The colon was the most common site of injury (n = 44; 76%), and transmural necrosis (n = 36; 62%) was the most common histopathologic lesion reported. Mortality was reported in 33% of these cases due to gastrointestinal injury.

CONCLUSIONS: Sodium polystyrene sulfonate use, both with and without sorbitol, may be associated with fatal gastrointestinal injury. Physicians must be cognizant of the risk of these adverse events when prescribing this therapy for the management of hyperkalemia.

 • The American Journal of Medicine (2013) 126, 264.e9-264.e24

KEYWORDS: Gastrointestinal adverse events; Hyperkalemia; Intestinal necrosis; Kayexalate; Sodium polystyrene sulfonate

Hyperkalemia is a common electrolyte disorder that if left untreated can result in fatal cardiac arrhythmias.[1] Successful management of hyperkalemia involves protecting the heart from arrhythmias, shifting potassium into the cells, and enhancing the elimination of potassium. Sodium polystyrene sulfonate (Kayexalate; Sanofi-Aventis, Paris, France) is a cation-exchange resin that is widely used in the management of hyperkalemia.[2-4] It exchanges sodium for potassium in the large bowel to promote potassium loss in the stool. Surprisingly, the evidence for its efficacy stems from a very weak level of evidence.

Sodium polystyrene sulfonate was approved by the Food and Drug Administration in 1958 after a case series report demonstrated a gradual decrease in serum potassium levels over a number of days in anuric patients who had hyperka-

Funding: None.

Conflict of Interest: None.

Authorship: All authors had access to the data and played a role in writing this manuscript.

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0002-9343/$ -see front matter
http://dx.doi.org/10.1016/j.amjmed.2012.08.016

lemia.[5] In its early use, sodium polystyrene sulfonate was administered as a suspension in water; however, concerns of constipation and life-threatening intestinal impaction led to the common practice of administering it with sorbitol, an osmotic laxative.[6] Although the addition of sorbitol to sodium polystyrene sulfonate minimized the rate of intestinal impaction, reports of fatalities related to necrosis of the terminal ileum and colon associated with its use were accumulating.[7,8]

The precise mechanism for gastrointestinal injury after sodium polystyrene sulfonate use is unknown; however, it is postulated that 70% sorbitol rather than sodium polystyrene sulfonate may be the culprit.[9] As a result, preparations of sodium polystyrene sulfonate containing 70% sorbitol have been removed from the market. Despite this, reports of similar injury have continued to occur with both preparations of sodium polystyrene sulfonate containing lower sorbitol concentrations and those without sorbitol.[10,11]

CLINICAL SIGNIFICANCE

- Kayexalate (Sanofi-Aventis, Paris, France) use with and without concomitant sorbitol is associated with gastrointestinal adverse events, including colonic necrosis.
- Risk factors for these adverse events include renal disease, transplantation, and the postoperative state.
- Physicians must be cognizant of the risk of adverse events when prescribing sodium polystyrene sulfonate therapy for the management of hyperkalemia and consider other safer agents when appropriate.

Despite a Food and Drug Administration black-box warning on its use with sorbitol and contention regarding its efficacy in reducing serum potassium levels, sodium polystyrene sulfonate continues to be widely prescribed for the management of acute and chronic hyperkalemia.[3,4,12-16] This practice may be placing patients at unnecessary risk. Until now, there have been no systematic attempts to identify and document cases of harm related to sodium polystyrene sulfonate use. Therefore, we aimed to systematically review reports of adverse gastrointestinal events associated with the use of sodium polystyrene sulfonate.

MATERIALS AND METHODS

This review was performed following the guidelines of Meta-analysis of Observational Studies in Epidemiology.[17]

Study Selection

We considered articles to be eligible for inclusion if they reported on a case or series of cases of gastrointestinal adverse events associated with sodium polystyrene sulfonate use. A gastrointestinal adverse event was defined as an unfavorable or harmful consequence involving the gastrointestinal tract related to the use of sodium polystyrene sulfonate. We excluded cases from further review if they fulfilled 1 or more of the following criteria: patients aged less than 18 years; patients with normal endoscopic/histologic findings on investigating the cause of gastrointestinal adverse events; and cases with a causality criteria of unlikely, conditional/unclassified, or unassessable/unclassifiable according to the World Health Organization (WHO) causality assessment criteria as described next.[18] We also excluded a case-series with missing information that could not be obtained from the authors.[19]

Causality Assessment Criteria

We used The World Health Organization–Uppsala Monitoring Center (WHO–UMC) causality assessment system to assess the likelihood of a causal relationship between sodium polystyrene sulfonate exposure and gastrointestinal adverse events for all eligible reports. The WHO–UMC causality assessment system is a validated and widely accepted method of pharmacovigilance that uses prespecified criteria to categorize the causal link between a drug and an adverse event into 1 of 6 discrete levels of certainty (certain, probable/likely, possible, unlikely, conditional/unclassified, and unassessable/unclassifiable) (**Appendix 1**). Given the severity of the adverse events associated with sodium polystyrene sulfonate use, we thought that most cases would fail to provide information on the effect of rechallenging patients with sodium polystyrene sulfonate, and thus fail to satisfy certain or probable/likely causality criteria. In light of this, we decided to include cases satisfying at minimum a possible level of certainty.

Literature Sources

We searched 3 electronic databases: OVID Medline (1948 to July 27, 2011), EMBASE (1980 to July 27, 2011), and the Cochrane Central Register of Controlled Trials (CENTRAL) (1993 to July 27, 2011) using a search strategy developed with an experienced health informatics specialist (**Appendix 2**). We applied no language restrictions and reviewed the bibliographies of identified articles to locate further eligible studies. In addition, we searched Google Scholar (586 hits), abstracts of the last 5 years from conferences of the American Society of Nephrology for relevant articles, and both the Health Canada Vigilance Adverse Reaction Online Database (1965 to July 27, 2011) and the Food and Drug Administration Adverse Event Reporting System (2004 to July 27, 2011). Where necessary, we contacted corresponding authors for additional missing data.

Data Abstraction

Two authors (ZH and SH) scanned titles and abstracts for initial selection. Selected articles were reviewed in full and independently assessed for eligibility and causality by the

same 2 reviewers. Discrepancies were resolved by consensus and involvement of other authors.

We abstracted the following data from each included article: baseline demographic characteristics (age, gender); comorbid conditions; admitting diagnosis; sodium polystyrene sulfonate dose, route, and duration of use; coadministration with sorbitol and where appropriate sorbitol concentration; presenting gastrointestinal symptoms after sodium polystyrene sulfonate administration; timing from initial sodium polystyrene sulfonate dose to symptoms; affected gastrointestinal segment; and clinical outcomes.

Statistical Analysis

We were aware that reports published in this area were case reports; thus, no meta-analysis was planned. We used descriptive statistics to compare differences between patients given sodium polystyrene sulfonate with and without sorbitol. Continuous variables were expressed as a mean (standard deviation) or median (interquartile range) and compared using an unpaired *t* test or Kruskal-Wallis test, respectively. Categoric variables were expressed as a percentage and compared using a chi-square test or Fisher exact test. We considered a *P* value less than .05 to be statistically significant. All statistical tests were conducted using SAS 9.2 (SAS Institute, Inc, Cary, NC).

RESULTS

We identified 553 relevant articles from our literature search. After applying our exclusion criteria, 30 articles describing 58 cases of adverse events were reported. These included 23 individual case reports[8,10,11,20-39] and 7 case series[7,9,40-44] (**Figure** and **Appendix 3**). Of the 58 reported cases in our review, 3 were reported before 1990, 24 were reported between 1990 and 2000, and 31 have been reported since 2000.

Patient Characteristics

Among patients who experienced gastrointestinal side effects, the mean age was 58 years, 50% were women, and 71% had a history of kidney disease (chronic kidney disease or end-stage renal disease requiring dialysis) as the predisposing factor for hyperkalemia. Sixteen percent of patients had a prior solid organ transplant, and 28% had recently undergone an operative procedure (**Table 1**).

Sodium polystyrene sulfonate was used for the management of acute hyperkalemia in 51 patients. Seven patients received sodium polystyrene sulfonate for more than 1 month. Sodium polystyrene sulfonate was administered via the oral route in 77% of cases, and multiple doses were given in 28 patients. Seventy-one percent of patients received sodium polystyrene sulfonate in combination with sorbitol. The concentration of sorbitol administered was reported in only 4 patients. Of these, 3 patients received a sodium polystyrene sulfonate preparation containing 20% sorbitol, and 1 patient received a 70% sorbitol preparation.

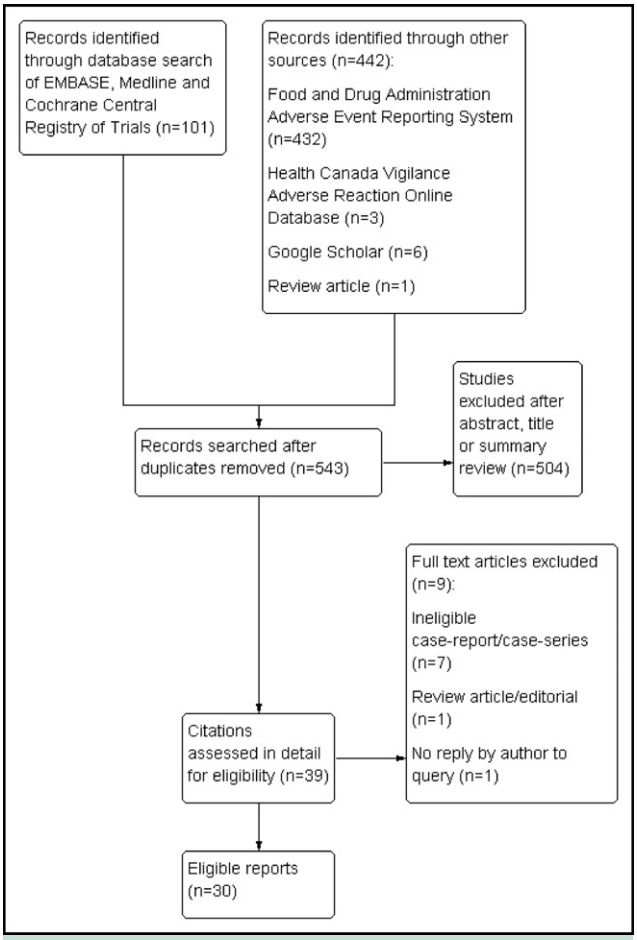

Figure Flow diagram of included studies.

The presenting gastrointestinal symptoms were abdominal pain and distension (n = 33), gastrointestinal bleeding (n = 13), diarrhea (n = 10), and nausea and vomiting (n = 6). The median time from the first sodium polystyrene sulfonate dose to the presentation of gastrointestinal symptoms was 2 days (interquartile range, <1-5 days).

Upper gastrointestinal injury associated with the use of sodium polystyrene sulfonate occurred in 2 patients, and lower gastrointestinal injury occurred in 56 patients. The colon was the most commonly affected segment of the gastrointestinal tract (n = 44) followed by the small intestine (n = 12). Histopathologic findings associated with sodium polystyrene sulfonate use were necrosis (n = 36) of the bowel wall, ulceration (n = 28), and perforation (n = 5). All patients had histopathologic examination of affected gastrointestinal segments, which demonstrated sodium polystyrene sulfonate crystals in 90% of patients.

For patients with gastrointestinal injury associated with sodium polystyrene sulfonate use, the overall mortality rate was 33%. Ninety-four percent of patients who died had colonic necrosis on biopsy.

Table 1 Characteristics of Included Studies

Characteristic	
Demographic	
Age, mean (SD)	58 ± 17
Female n (%)	29 (50)
Comorbidities, n (%)	
Chronic kidney disease	15 (26)
ESRD requiring dialysis	26 (45)
Transplant	9 (16)
Coronary artery disease	9 (16)
Peripheral vascular disease	5 (9)
Hypertension	24 (41)
Diabetes	8 (14)
Current hospitalization, n (%)	
Postoperative	16 (28)
Acute kidney injury	12 (21)
Kayexalate treatment, n (%)	
Single dose*	5 (15)
Chronic doses	7 (12)
Concomitant sorbitol	41 (71)
Route†	
Oral route	58 (77)
Per rectum	15 (20)
Nasogastric	2 (3)
Presenting symptoms, n (%)	
Abdominal pain or tenderness	33 (57)
Nausea/vomiting	6 (11)
Blood per rectum	13 (24)
Diarrhea	10 (18)
Time to symptoms‡ (after first SPS dose), in days, median (IQR) (nonchronic doses)	2 (<1-5)
GI involvement of injury, n (%)	
Esophagus	1 (2)
Stomach	2 (3)
Small bowel	12 (21)
Cecum	6 (10)
Colon	44 (76)
Sigmoid/rectum/anus	9 (16)
Histopathology of injury, n (%)	
Necrosis	36 (62)
Ulceration	28 (48)
Perforation	5 (9)
SPS crystals	52 (90)
Outcome, n (%)	
Alive	33 (57)
Death	19 (33)
Not reported	6 (10)

ESRD = end-stage renal disease; GI = gastrointestinal; IQR = interquartile range; SD = standard deviation; SPS = sodium polystyrene sulfonate.

*A total of 33 cases reported single versus multiple dose.

†Among 75 cases reporting number of doses and route.

‡Among 5 reported cases in the SPS without sorbitol group and 24 reported cases in the sorbitol group.

Sodium Polystyrene Sulfonate With Sorbitol Versus Without Sorbitol

Compared with patients receiving concomitant sorbitol therapy, those receiving sodium polystyrene sulfonate without sorbitol were more likely to be chronic users ($P < .01$), to have received an oral formulation ($P < .01$), and to have presented with abdominal pain ($P = .03$). However, patients receiving sodium polystyrene sulfonate with sorbitol were more likely to receive sodium polystyrene sulfonate by a rectal enema ($P = .01$) and to have bowel necrosis on histopathologic examination ($P = .01$). There were no other features that distinguished patients who received sodium polystyrene sulfonate sorbitol versus sodium polystyrene sulfonate without sorbitol (**Table 2**).

Causality Assessment

All included cases met WHO–UMC causality criteria for a possible causal link between sodium polystyrene sulfonate and gastrointestinal adverse events. Criteria for a certain or probable/likely causal relationship could not be met because information on the response to withdrawal of sodium polystyrene sulfonate was not described, nor was the effect of rechallenging patients with sodium polystyrene sulfonate for any case.

DISCUSSION

Our review of case series and case reports with standardized causality assessment identified 58 cases of possible severe gastrointestinal adverse events associated with sodium polystyrene sulfonate use. These events occurred in the context of sodium polystyrene sulfonate use with and without concomitant sorbitol-containing preparations and most commonly affected the lower gastrointestinal tract.

Previous reports have suggested that numerous risk factors, including chronic kidney disease, end-stage renal disease, solid organ transplantation, and postoperative status, contribute to gastrointestinal injury associated with sodium polystyrene sulfonate use through various mechanisms.[7,9,41,43,44] Indeed, we identified that a number of these risk factors were present in a majority of cases reviewed in this article. Most notably, 91% of cases included in this review had a history of acute kidney injury, chronic kidney disease, or end-stage renal disease. Patients with renal diseases have elevated renin levels, which predispose them to nonocclusive mesenteric ischemia through angiotensin II–mediated vasoconstriction.[45] As observed from our results, this risk may be increased in the postoperative period, which may be due to concomitant hypotension, ileus-induced colonic distension (resulting in reduced colonic blood flow), and decreased gut motility as a result of opioids, uremia, and constipation.[23,42] Patients who recently underwent transplantation are at particularly increased risk of such complications as a result of immunosuppressive medications that impair the normal protective and reparative mechanisms of gastrointestinal cells.[46] These pathophysiologic processes may be potentiated by the concomitant use of sorbitol with sodium polystyrene sulfonate.[9]

Sorbitol is believed to directly damage intestinal mucosa, leading to vasospasm, exacerbation of inflammation through elevated prostaglandin levels, and ultimately vascular injury.[9]

Table 2 Characteristics of Reported Cases of Sodium Polystyrene Sulfonate With Sorbitol Versus Sodium Polystyrene Sulfonate Without Sorbitol

Variable	SPS With Sorbitol (n = 41)	SPS Without Sorbitol (n = 17)	*P* Value
Demographic			
Age, mean (SD)	58 ± 18	58 ± 16	.92
Female, n (%)	19 (46)	10 (59)	.38
Comorbidities, n (%)			
Chronic kidney disease	10 (24)	5 (29)	.75
ESRD requiring dialysis	19 (46)	7 (41)	.72
Transplant	7 (17)	2 (12)	.71
Coronary artery disease	8 (19)	2 (12)	.71
CVD	1 (2)	4 (24)	.02*
Hypertension	19 (46)	5 (29)	.23
Diabetes	8 (20)	2 (12)	.71
Current hospitalization, n (%)			
Postoperative	13 (32)	3 (18)	.34
Acute kidney injury	7 (17)	5 (29)	.48
SPS treatment, n (%)			
Single dose†	4 (23)	1 (6)	.33
Chronic dose	0 (0)	7 (41)	<.01*
Route‡			
Oral route	40 (71)	18 (95)	.05*
Per rectum	14 (25)	1 (5)	.01*
Nasogastric	2 (4)	0 (0)	1
Presenting symptoms, n (%)			
Abdominal pain/tenderness	21 (51)	13 (76)	.74
Nausea/vomiting	2 (5)	4 (24)	.06
GI bleed	9 (22)	5 (29)	.74
Diarrhea	3 (7)	8 (47)	.18
Time to symptoms (after first SPS dose), in days, median (IQR) (nonchronic doses)§	1.5 (<1-3)	5 (<1-25)	.27
GI involvement of injury, n (%)			
Esophagus	1 (2)	0 (0)	1
Stomach	2 (5)	0 (0)	.58
Small bowel	11 (27)	1 (6)	.09
Cecum	4 (10)	2 (12)	1
Colon	33 (80)	12 (71)	.49
Sigmoid/rectum/anus	4 (10)	5 (29)	.1
Histopathology of injury, n (%)			
Necrosis	30 (73)	7 (41)	.01*
Ulceration	12 (29)	9 (53)	.09
Perforation	3 (7)	2 (13)	.62
SPS crystals	38 (93)	14 (82)	.34
Outcome, n (%)			
Alive	22 (54)	11 (65)	.43
Death	15 (36)	4 (24)	.33
Not reported	4 (10)	2 (12)	1

CVD = cardiovascular disease; ESRD = end-stage renal disease; GI = gastrointestinal; IQR = interquartile range; SD = standard deviation; SPS = sodium polystyrene sulfonate.

*Statistical significance.

†Among 17 reported cases in the SPS with sorbitol group and 16 cases in the SPS without sorbitol group.

‡Among 56 cases reporting number of doses and route in the SPS with sorbitol group and 19 cases in the SPS without sorbitol group.

§Among 24 reported cases in the SPS with sorbitol group and 5 reported cases in the SPS without sorbitol group.

The resulting histopathologic lesions vary from patchy inflammation to frank necrosis.[9] These findings were supported by our review, which demonstrated a spectrum of injury among cases given sodium polystyrene sulfonate with sorbitol. Furthermore, sodium polystyrene sulfonate crystals were commonly found aggregated within the in-

jured areas of the gastrointestinal tract histopathologic specimens. Although previous reports have attributed the majority of gastrointestinal adverse events to 70% sorbitol-sodium polystyrene sulfonate preparations, we identified only 1 report associated with this concentration, because the majority of reports failed to describe the concentration of sorbitol used.[12,13]

Our review included a number of cases of patients using sodium polystyrene sulfonate in the absence of sorbitol who experienced similar gastrointestinal adverse events. Although previous reports of sodium polystyrene sulfonate–induced gastrointestinal injury have alluded to the fact that the presence of sodium polystyrene sulfonate crystals in injured segments of the gastrointestinal tract may represent a "footprint" of its use, our report suggests that sodium polystyrene sulfonate itself may be pathogenic. Work by Haupt and Hutchins[47] has demonstrated that inoculation of tissue with sodium polystyrene sulfonate leads to the development of an acute inflammatory reaction within 24 hours. In the gastrointestinal tract of susceptible individuals, such as those with chronic kidney disease or vascular disease, and solid organ transplant recipients, the elaboration of inflammatory cytokines and prostaglandins may lead to further impairment in local hemodynamic mechanisms leading to vascular injury and subsequent mucosal injury.[9] Given our results, the pathogenesis of bowel injury related to sodium polystyrene sulfonate use is likely more complex than our current understanding and may represent a histopathologic pattern of injury in response to a wide variety of heterogeneous insults.

Although the colon is the most common location of injury, it is increasingly recognized that injury from sodium polystyrene sulfonate may occur in more proximal sections of the gastrointestinal tract.[19,42] In keeping with this finding, our review shows that approximately 30% of cases present with an injury appearing in the esophagus, stomach, or small intestine. A majority of these cases do have concurrent colonic injury. This change may reflect a trend favoring the use of oral, as opposed to rectal sodium polystyrene sulfonate. However, irrespective of the location of sodium polystyrene sulfonate–associated injury induced, mortality remains high. The increased mortality may be a consequence of the severity of the injury in addition to the large comorbid disease burden of affected patients.

Our review has several strengths. It is the first review describing safety problems associated with use of sodium polystyrene sulfonate, both with and without concomitant sorbitol. We used a broad search strategy and included published and unpublished sources to capture all safety events. Finally, we also used standardized criteria to assess for causality.

Our study also has several limitations. All findings were drawn from case reports and case series. As is the case in other reports concerning suspected adverse drug reactions, our review cannot ensure that the relationship between sodium polystyrene sulfonate and the described gastrointestinal adverse events is certain. However, the use of the WHO–UMC criteria for causality assessment allows for a qualitative assessment of relationship likelihood based on the available evidence. Furthermore, the use of the WHO–UMC criteria decreased disagreements between the 2 assessors by providing a methodological framework for evaluation of adverse events related to sodium polystyrene sulfonate use.

Second, our review was limited by incomplete information, the lack of a standardized method of reporting adverse events, and possible selection and publication biases. Although we attempted to increase the applicability and generalizability of our findings by accessing reports from 2 national regulatory agencies, the descriptions were not sufficiently detailed for inclusion, and therefore cases may have been missed.

Third, because of the lack of a proper denominator, we were unable to calculate attributable risk associated with sodium polystyrene sulfonate. As such, this report is not able to estimate actual risk of gastrointestinal effects because we have no numbers available as to the prevalence of the use of sodium polystyrene sulfonate. Because sodium polystyrene sulfonate is so widely prescribed (~5 million doses prescribed yearly in the United States), the potential risk for adverse gastrointestinal events may be even greater than currently appreciated.[12]

Finally, sodium polystyrene sulfonate–related adverse gastrointestinal events that are subtle in nature likely never reached clinical detection, thereby limiting efforts to quantify the incidence of these events and evaluate risk factors.

Thus far, evidence corroborating the effectiveness of sodium polystyrene sulfonate in treating hyperkalemia is weak and based on results from small case series that may not be generalizable to contemporary patient populations.[5,6,48] Although the incidence of sodium polystyrene sulfonate–mediated intestinal injury has been estimated to be 1.8%,[40] the widespread availability of safer, potentially more effective treatments for managing hyperkalemia have led some to question its use in the management of hyperkalemia.[3,12,49,50] Ultimately, a randomized control trial evaluating the efficacy and safety of sodium polystyrene sulfonate alone and combination with other strategies that promote potassium loss (eg, loop diuretics, conventional laxatives) in managing severe hyperkalemia is needed to conclusively demonstrate the role of sodium polystyrene sulfonate in the management of hyperkalemia.

CONCLUSIONS

The use of sodium polystyrene sulfonate in the treatment of hyperkalemia may be associated with serious gastrointestinal adverse events. Although the risk to an individual patient may not be high, the widespread use of this medication may be exposing a large population to potential risk, especially in light of other alternatives. Although hyperkalemia-associated deaths are preventable with effective reduction in serum potassium, rigorous assessment of the optimal strat-

egy, both in terms of safety and efficacy, is needed. Until then, physicians must be cognizant of the risk of these adverse events when prescribing sodium polystyrene sulfonate therapy for the management of hyperkalemia.

ACKNOWLEDGMENTS

The authors thank Dr Kamel S. Kamel, MD, of St Michael's Hospital, University of Toronto, for the critical review of the manuscript and Elizabeth Uleryk, MLS, of The Hospital for Sick Children, University of Toronto, for help with the literature search.

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Appendix 1 World Health Organization–Uppsala Monitoring Center Causality Criteria

Causality Term	Assessment Criteria
Certain	Event or laboratory test abnormality, with plausible time relationship to drug intake; cannot be explained by disease or other drugs; (iii) response to withdrawal plausible (pharmacologically, pathologically); (iv) event definitive pharmacologically or phenomenologically (ie, an objective and specific medical disorder or a recognized pharmacologic phenomenon); (v) rechallenge satisfactory, if necessary
Probable/likely	(i) Event or laboratory test abnormality, with reasonable time relationship to drug intake; unlikely to be attributed to disease or other drugs; response to withdrawal clinically reasonable; rechallenge not required.
Possible	Event or laboratory test abnormality, with reasonable time relationship to drug intake; could also be explained by disease or other drugs; information on drug withdrawal may be lacking or unclear
Unlikely	Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible); disease or other drugs provide plausible explanations
Conditional/unclassified	Event or laboratory test abnormality; more data for proper assessment needed or additional data under examination
Unassessable/unclassifiable	Report suggesting an adverse reaction; cannot be judged because information is insufficient or contradictory; (iii) data Cannot be supplemented or verified

Appendix 2 Search Strategy

Database: Ovid MEDLINE(R) <1948 to July Week 2 2011>
Search Strategy:
1 (kalexate or kayexalate or kionex or "poly sodium styrene sulfonate" or "polystyrene sodium sulfonate" or "polystyrene sulfonate sodium" or resinsodio or resonium or resonium or "sodium polystyrene sulfonate").mp. (169)
2 necrosis/or ((bowel or colon* or intestin* or gut) adj2 (necrosis or necrot*)).ti,ab. (46981)
3 1 and 2 (25)
4 exp Sorbitol/or (yal or "klysma sorbit" or "glucitol" or sorbilax or sorbitol or medevac).mp. (17845)
5 1 and 4 (32)
6 3 or 5 (38)

Database: Embase <1980 to 2011 Week 29>
Search Strategy:
10 polystyrenesulfonate sodium/or (kalexate or kayexalate or kionex or "poly sodium styrene sulfonate" or "polystyrene sodium sulfonate" or "polystyrene sulfonate sodium" or resinsodio or resonium or resonium or "sodium polystyrene sulfonate").mp. (816)
11 necrosis/or intestine necrosis/or mucosal necrosis/or necrotizing enteritis/or necrotizing enterocolitis/or necrotizing esophagitis/or ((bowel or colon* or intestin* or gut) adj2 (necrosis or necrot*)).ti,ab. (37887)
12 10 and 11 (47)
13 sorbitol/or (yal or "klysma sorbit" or "glucitol" or sorbilax or sorbitol or medevac). mp. (11299)
14 10 and 13 (79)
15 12 or 14 (95)

Database: EBM Reviews—Cochrane Central Register of Controlled Trials <3rd Quarter 2011>
Search Strategy:
1 polystyrenesulfonate sodium/or (kalexate or kayexalate or kionex or "poly sodium styrene sulfonate" or "polystyrene sodium sulfonate" or "polystyrene sulfonate sodium" or resinsodio or resonium or resonium or "sodium polystyrene sulfonate").mp. (8)

Appendix 3 Characteristics of Included Studies

Study	Age (y), Sex	Admitting Diagnosis	Comorbid Conditions	Total No. of Doses of SPS (± Sorbitol)	SPS Dose and Route	Sorbitol Concentration	Presenting Symptoms	Time From First SPS Dose to Symptoms (d)	Affected Segment of the GI Tract	Histopathology	Outcome	WHO Causality Category
Arvanitakis et al[7] 1973	33, F	Renal transplantation	ESRD on dialysis	Not specified; SPS only	Not specified; PO	Not applicable	Abdominal pain; bloody diarrhea; fever	Not specified	Colon	Inflammatory changes with ulceration	Alive	Possible
	18, M	Renal transplantation	ESRD on dialysis; Alport's syndrome	3; SPS only	60 g × 3; PO	Not applicable	Abdominal pain; bloody diarrhea	Not specified	Rectum	Hemorrhagic proctitis	Alive	Possible
Wootton et al[8] 1989	48, M	Renal transplantation	ESRD on dialysis	4; all sorbitol	(i) 1 × 50 g; PR ii) 3 × not specified; PR	(i) 20% (ii) Not specified	Abdominal pain and fever	1	Transverse colon	Transmural infarction; SPS crystals in submucosa	Alive	Possible
Gerstman et al[40] 1992	43, M	Transplant nephrectomy	ESRD on dialysis; renal transplant	1; with sorbitol	50 g; PO	Not specified	Abdominal pain	2	Cecum; right colon	Necrotic cecum	Alive	Possible
	42, M	Cardiac transplant	Not specified	7; with sorbitol	(i) 2 × 15 g (day 6) (ii) 3 × 15 g (day 7) (iii) 2 × 30 g (day 8) all PO	Not specified	Abdominal pain	<1	Cecum; small bowel; right colon	Edematous small bowel and right colon; distended cecum	Alive	Possible
Scott et al[20] 1993	48, M	Renal transplantation	ESRD on dialysis; HTN	1; with sorbitol	50 g; PO	20%	Abdominal pain and distention	<1	Colon	Colonic necrosis; SPS crystals (location not reported)	Alive	Possible
Gardiner[41] 1997	66, M	Aortic valve replacement	Not specified	Not specified; with and without sorbitol	(i) Not specified PR (without sorbitol) (ii) 240 g NG (with sorbitol)	Not specified	Not specified	6	Stomach; ileum; colon	Mucosal erosions; transmural inflammation and necrosis; SPS crystals in submucosa	Death	Possible
	71, F	Lower GI bleed	CKD; DM	Not specified; SPS only (chronic)	15 g/d; PO	Not applicable	Lower GI bleed	Not specified	Right colon	Mucosal necrosis; transmural inflammation; SPS crystals in submucosa	Death	Possible
Roy-Chaudhury et al[21] 1997	42, F	Left acetabular graft revision	ESRD on dialysis	5 total: 3 with sorbitol 2 SPS only	(i) 2 × 50 g; PO (sorbitol) ii) 3 × 30 g; PO (SPS only)	(i) 20%	Abdominal pain and distention	1	Terminal ileum; right colon	Ileal transmural necrosis; ileal/cecal perforation; SPS crystals in necrotic tissue	Alive	Possible

Appendix 3 Continued

Study	Age (y), Sex	Admitting Diagnosis	Comorbid Conditions	Total No. of Doses of SPS (± Sorbitol)	SPS Dose and Route	Sorbitol Concentration	Presenting Symptoms	Time From First SPS Dose to Symptoms (d)	Affected Segment of the GI Tract	Histopathology	Outcome	WHO Causality Category
Lillemoe et al[9] 1997	40, F	Nephrectomy	ESRD on dialysis; HTN	1; all sorbitol	1 × not specified; PR	Not specified	Abdominal pain; shock	3	Ileum; colon	Transmural infarction; SPS crystals (location not reported)	Alive	Possible
	52, M	CABG	ESRD on dialysis; CAD	3; all sorbitol	3 × not specified; PR	Not specified	Abdominal pain; fever	Not specified	Colon	Transmural infarction of colon and rectum; SPS crystals (location not reported)	Death	Possible
	31, M	AV valve repair	Transposition of the great vessels	4; all sorbitol	(i) 3 × not specified; PO (ii) 1 × not specified; PR	Not specified	Abdominal pain and distention; fever	<1	Colon; terminal ileum	Transmural infarction of colon and terminal ileum; SPS crystals (location not reported)	Death	Possible
	36, M	Acute kidney injury; weight loss	Renal transplant	2; all sorbitol	(i) 1 × not specified; PO (ii) 1 × not specified; PR	Not specified	Abdominal distention; diarrhea; fever	1	Colon	Mucosal and transmural infarction of colon and cecum; SPS crystals (location not reported)	Death	Possible
Rashid and Hamilton[42] 1997	60, M	Not specified	CAD; CKD; HTN; EtOH cirrhosis	Not specified; all sorbitol	30 g total dose; NG	Not specified	Abdominal pain	Not specified	Ileum; pancolic; rectum	Mucosal ulcers; transmural necrosis; rectal mucosal necrosis; SPS crystals (location not reported)	Death	Possible
	77, F	Not specified	Cervical carcinoma; COPD	Not specified; all sorbitol	Not specified	Not specified	GI bleed	Not specified	Colon	Mucosal and focal transmural necrosis; mucosal necrosis of terminal ileum	Death	Possible
	54, M	Not specified	ESRD on dialysis; hepatitis; PE	Not specified; all sorbitol	Not specified	Not specified	GI bleed	Not specified	Colon	Mucosal ulcers; pseudomembranes; transmural necrosis; perforation; SPS crystals (location not reported)	Death	Possible

Appendix 3 Continued

Study	Age (y), Sex	Admitting Diagnosis	Comorbid Conditions	Total No. of Doses of SPS (± Sorbitol)	SPS Dose and Route	Sorbitol Concentration	Presenting Symptoms	Time From First SPS Dose to Symptoms (d)	Affected Segment of the GI Tract	Histopathology	Outcome	WHO Causality Category
	72, F	Not specified	ESRD on dialysis; COPD; HTN	Not specified; all sorbitol	60 g total dose; PO	Not specified	GI bleed	Not specified	Small intestine; colon	Transmural necrosis; cholesterol emboli; SPS crystals (location not reported)	Death	Possible
	49, F	Not specified	ESRD on dialysis; HTN	Not specified; all sorbitol	30 g total dose; PO	Not specified	Abdominal pain and vomiting	Not specified	Right colon	Mucosal psuedomembrane and transmural edema; SPS crystals (location not reported)	Alive	Possible
	61, M	Not specified	ESRD on dialysis; DM; HTN	Not specified; all sorbitol	120 g total dose; PO	Not specified	GI bleed	Not specified	Sigmoid colon	Mucosal ulcers; SPS crystals (location not reported)	Alive	Possible
	31, F	Not specified	ESRD on dialysis; renal transplant	Not specified; all sorbitol	20 g total dose; PO	Not specified	GI bleed	Not specified	Cecum	Mucosal ulcers; SPS crystals (location not reported)	Not reported	Possible
	36, M	Not specified	ESRD on dialysis; MGUS	Not specified; all sorbitol	Not specified	Not specified	GI bleed	Not specified	Gastric remnants	Hemorrhagic gastritis; SPS crystals (location not reported)	Alive	Possible
	65, F	Not specified	CKD; Sjögren's syndrome	Not specified; all sorbitol	20 g total dose; PO	Not specified	GI bleed	Not specified	Colon	Pseudomembranes and transmural necrosis; SPS crystals (location not reported)	Death	Possible
	66, M	Not specified	ESRD on dialysis; HTN; COPD	Not specified; all sorbitol	Not specified	Not specified	GI bleed	Not specified	Colon	Diverticulitis with SPS crystals in diverticuli	Not reported	Possible
	60, M	Not specified	Liver transplant; CKD; DM; COPD	Not specified; all sorbitol	15 g total dose; PO	Not specified	Abdominal pain	Not specified	Colon	Mild crypt distortion; SPS crystals (location not reported)	Alive	Possible
	66, M	Not specified	CKD; iron deficiency	Not specified; all sorbitol	20 g total dose; PO	Not specified	Abdominal pain and vomiting	Not specified	Esophagus	Esophageal ulcer; SPS crystals (location not reported)	Alive	Possible

Appendix 3 Continued

Study	Age (y), Sex	Admitting Diagnosis	Comorbid Conditions	Total No. of Doses of SPS (± Sorbitol)	SPS Dose and Route	Sorbitol Concentration	Presenting Symptoms	Time From First SPS Dose to Symptoms (d)	Affected Segment of the GI Tract	Histopathology	Outcome	WHO Causality Category
Schiere et al[22] 1997	67, M	Ruptured aortic aneurysm	HTN; TIA	5 total: 2 with sorbitol 3 SPS only	(i) 15 g; PR (day 3 with sorbitol) (ii) 25 g; PR (day 12 with sorbitol) (iii) 3 × 10 g; PO (days 15-18; SPS only)	Not specified	Lower GI bleed	5	Colon	Mucosal ulceration; SPS crystals (location not reported)	Alive	Possible
Dardik et al[23] 2000	61, M	Weakness	CKD; bipolar disorder; pancreatitis	2; all sorbitol	(i) 1 × not specified; PO (ii) 1 × not specified; PR	Not specified	Abdominal pain and fever	1	Transverse colon	Transmural necrosis; pseudomembranes; superficial ulceration; SPS crystals (location not reported)	Alive	Possible
Rogers and Li[24] 2001	55, M	Decreased level of consciousness; AKI	Stroke	Not specified; SPS only	Not specified; PR	Not applicable	Abdominal pain; lower GI bleed	5	Rectosigmoid colon	Transmural necrosis; SPS crystals in ulcer bed	Alive	Possible
Cheng et al[37] 2002	53, F	Burn injury	Not specified	2; SPS only	2 × 15 g; PO	Not applicable	Abdominal pain; nausea and vomiting; diarrhea	1	Splenic flexure	Transmural penetration; deep ulcers with intramural necrosis; SPS crystals (location not reported)	Death	Possible
Montagnac et al[43] 2002	63, F	Abdominal pain and chronic constipation	ESRD on dialysis; hepatitis C; HTN; CVD	Not specified; SPS only (chronic)	30 mL/d; PO	Not applicable	Abdominal pain; lower GI bleed; diarrhea	Not specified	Colon	Colonic ulcers; SPS crystals(location not reported)	Alive	Possible
	72, F	Abdominal pain and chronic constipation	ESRD on dialysis; HTN; dyslipidemia	Not specified; SPS only (chronic)	30 mL/d; PO	Not applicable	Abdominal pain; vomiting	Not specified	Colon	Colonic ulcers; SPS crystals (location not reported)	Alive	Possible
Mulder et al[25] 2002	44, M	Abdominal pain	Renal transplant	Not specified; SPS only (chronic)	15 g/d; PO	Not applicable	Abdominal pain	Not specified	Sigmoid colon	Chronic inflammation; SPS crystals (location not reported)	Alive	Possible
Kelsey et al[26] 2003	79, M	Vascular access occlusion	ESRD on dialysis; CAD; COPD; PVD	2; with sorbitol	2 × 60 g; PO	Not specified	Abdominal pain and distention	4	Ileum; right colon	Transmural necrosis and mucosal ulceration; SPS crystals in ulcers	Alive	Possible

Appendix 3 Continued

Study	Age (y), Sex	Admitting Diagnosis	Comorbid Conditions	Total No. of Doses of SPS (± Sorbitol)	SPS Dose and Route	Sorbitol Concentration	Presenting Symptoms	Time From First SPS Dose to Symptoms (d)	Affected Segment of the GI Tract	Histopathology	Outcome	WHO Causality Category
Hourseau et al[11] 2004	64, M	Serratia sepsis	ESRD on dialysis; HTN	Not specified; SPS only (chronic)	Not specified; PO	Not applicable	Diarrhea	Not specified	Colon; rectum	Ulcer; acute inflammation rectal mucosa; SPS crystals(location not reported)	Death	Possible
Mordi et al[38] 2005	60, M	Abdominal pain and fever	ESRD on dialysis; autoimmune disease on steroids; CAD	Not specified; SPS only (chronic)	Not specified	Not applicable	Abdominal pain and fever	Not specified	Colon; sigmoid colon	Necrotizing colitis; SPS crystals (location not reported)	Alive	Possible
van der Valk et al[27] 2006	66, M	Constipation; abdominal pain	ESRD on dialysis	Not specified; SPS only (chronic)	15 g/d; PO	Not applicable	Abdominal pain and distention	Not specified	Ileum	Ulceration; perforation; SPS crystals (location not reported)	Death	Possible
Mummadi et al[28] 2007	39, M	Syncope	ESRD on dialysis	1; with sorbitol	30 g × 1; PO	Not specified	Abdominal pain	<1	Terminal ileum; cecum	Terminal ileal necrosis; cecal perforation; SPS crystals (location not reported)	Not reported	Possible
Teshima et al[29] 2007	75, F	Inflammatory arthritis; AKI	CKD	2; with sorbitol	Not specified; PO	Not specified	Rectal bleed	Not specified	Colon	Mucosal necrosis; SPS crystals in mucosa	Not reported	Possible
Chatelain et al[36] 2007	46, M	Polytrauma	None	5; SPS only	30 g × 5; PO	Not applicable	Not specified	5	Left colon	Colonic ulcers and ischemic colitis; transmural necrosis, SPS crystals in submucosa	Alive	Possible
Trottier et al[31] 2009	24, F	Elective seizure workup	Seizure disorder	3; with sorbitol	(i) 2 × 30 g; NG (ii) 1 × 50 g; PR	Not specified	Abdominal pain and distention	12	Ileum	Ileal ulcer and transmural necrosis; SPS crystals within the ulcers	Alive	Possible
Douglas et al[39] 2008	55, M	Scrotal cellulitis	Renal transplant; ESRD on dialysis	3; with sorbitol	Not specified; PO	Not specified	Abdominal pain; diarrhea; fever	2	Ileum; colon	Extensive mucosal necrosis; SPS crystals (location not reported)	Death	Possible
Bomback et al[30] 2009	56, F	Epigastric pain	CKD; DM; CAD; CVA	1; SPS only	15 g; PO	Not applicable	Not specified	Not specified	Transverse colon	Colonic necrosis; SPS crystals in mucosa	Alive	Possible

Appendix 3 Continued

Study	Age (y), Sex	Admitting Diagnosis	Comorbid Conditions	Total No. of Doses of SPS (± Sorbitol)	SPS Dose and Route	Sorbitol Concentration	Presenting Symptoms	Time From First SPS Dose to Symptoms (d)	Affected Segment of the GI Tract	Histopathology	Outcome	WHO Causality Category
Tapia et al[32] 2009	71, F	Congestive heart failure	CKD	4; SPS only	4 × 20 g; PO	Not applicable	Abdominal pain; diarrhea; vomiting	10	Cecum; left colon	Ischemic colitis; segmental ulcers; SPS crystals (location not reported)	Alive	Possible
Thomas et al[10] 2009	64, F	Pulmonary infection/ pulmonary edema	Afib; stroke	3; SPS only	3 × 90 g; PO	Not applicable	Abdominal pain and distention	<1	Distal colon	Ulcerated mucosa; SPS crystals in mucosa	Alive	Possible
McGowan et al[44] 2009	62, M	Rectal bleeding	ESRD on dialysis; CAD; HTN	Not specified; all sorbitol	170 g total dose; not specified	Not specified	Not specified	<1	Right colon; splenic flexure	Colonic mucosa with active inflammation; focal ulceration and granulation tissue; SPS crystals (location not reported)	Alive	Possible
	83, F	Chest pain	CAD; HTN; COPD; dyslipidemia	Not specified; all sorbitol	120 g total dose; not specified	Not specified	Not specified	2	Pancolon	Transmural necrosis; SPS crystals (location not reported)	Death	Possible
	63, F	Pancreatitis	CAD; HTN; DM2; dyslipidemia; pancreatitis	Not specified; all sorbitol	120 g total dose; not specified	Not specified	Not specified	1	Right colon	Ulcerated mucosa and focal necrosis; SPS crystals (location not reported)	Alive	Possible
	78, F	Pelvic fracture	ESRD on dialysis; CAD; HTN; AFib	Not specified; all sorbitol	60 g total dose; not specified	Not specified	Not specified	<1	Rectosigmoid colon	Acute colitis; SPS crystals (location not reported)	Alive	Possible
	83, F	COPD exacerbation	CAD; HTN; COPD; dyslipidemia; CHF	Not specified; all sorbitol	135 g total dose; not specified	Not specified	Not specified	2	Small intestine	Transmural necrosis and perforation; SPS crystals (location not reported)	Death	Possible
	75, F	Pneumonia	CAD; HTN; dyslipidemia; CKD; DM2	Not specified; all sorbitol	60 g total dose; not specified	Not specified	Not specified	3	Right colon	Focal necrosis; SPS crystals (location not reported)	Alive	Possible
	30, F	Depression	ESRD on dialysis; SLE	Not specified; all sorbitol	90 g total dose; not specified	Not specified	Not specified	<1	Pancolon	Diffuse transmural necrosis; SPS crystals (location not reported)	Death	Possible

Appendix 3 Continued

Study	Age (y), Sex	Admitting Diagnosis	Comorbid Conditions	Total No. of Doses of SPS (± Sorbitol)	SPS Dose and Route	Sorbitol Concentration	Presenting Symptoms	Time From First SPS Dose to Symptoms (d)	Affected Segment of the GI Tract	Histopathology	Outcome	WHO Causality Category
	91, F	Pneumonia	HTN; CKD	Not specified; all sorbitol	30 g total dose; not specified	Not specified	Not specified	5	Rectum	Ulcerated mucosa; SPS crystals (location not reported)	Alive	Possible
	85, F	COPD exacerbation	HTN; COPD	Not specified; all sorbitol	45 g total dose; not specified	Not specified	Not specified	3	Left colon	Mucosal necrosis; SPS crystals (location not reported)	Death	Possible
	59, F	Knee replacement	HTN; CKD; adrenal insufficiency	Not specified; all sorbitol	Not specified	Not specified	Not specified	11	Small intestine; right and transverse colon	Segmental ischemic necrosis, focally transmural with perforation; SPS crystals (location not reported)	Alive	Possible
	70, F	Rectal bleeding	ESRD on dialysis; HTN; DM2	Not specified; all sorbitol	Not specified	Not specified	Not specified	Not specified	Right colon	Necrotic mucosa; SPS crystals (location not reported)	Alive	Possible
Erfani et al[33] 2010	70, F	Suprapubic pain; dysuria	CKD; DM; HTN; CHF; bipolar disorder	5; all sorbitol	5 × not specified; PO	Not specified	Abdominal pain	Not specified	Ascending colon	Ulceration and necrosis; SPS crystals in submucosa	Not reported	Possible
Albino et al[34] 2011	75, F	Not specified	CKD; HTN; PVD	3; with sorbitol	15 g × 3; PO	Not specified	Abdominal pain; bloody diarrhea	1	Colon	Mucosal necrosis; SPS crystals (location not reported)	Not reported	Possible
Chou et al[35] 2011	30, M	Lower GI bleed	ESRD on dialysis; HTN; ureteral carcinoma	2 total: 1with sorbitol 1 SPS only	(i) 1 × 30 g; PO (sorbitol) (ii) 1 × 60 g; PR (SPS only)	70%	Ongoing lower GI bleed	Not specified	Transverse colon; splenic flexure	Necrotic ulcers; eroded mucosa; SPS crystals in ulcerated debris	Alive	Possible

AFib = atrial fibrillation; AKI = acute kidney injury; AV = aortic valve; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CHF = congestive heart failure; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CVA = cerebrovascular accident; CVD = cerebrovascular disease; DM = diabetes mellitus; ESRD = end-stage renal disease; EtOH = ethanol; GI = gastrointestinal; HTN = hypertension; MGUS = monoclonal gammopathy of unknown significance; NG = nasogastric; PE = pulmonary embolism; PO = per os, PR = per rectum; PVD = peripheral vascular disease; SLE = systemic lupus erythematous; SPS = sodium polystyrene sulphonate; TIA = transient ischemic attack; WHO = World Health Organization.