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Intestinal Necrosis due to Sodium Polystyrene Sulfonate (Kayexalate) in Sorbitol

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Abstract

Background—Sodium polystyrene sulfonate (SPS, Kayexalate) has been implicated in the development of intestinal necrosis. Sorbitol, added as a cathartic agent, may be primarily responsible. Previous studies have documented bowel necrosis primarily in postoperative, dialysis, and transplant patients. We sought to identify additional clinical characteristics among patients with probable SPS-induced intestinal necrosis.

Methods—Rhode Island Hospital surgical pathology records were reviewed to identify all gastrointestinal specimens reported as containing SPS crystals from December 1998 to June 2007. Patient demographics, medical comorbidities, and hospital courses of histologically verified cases of intestinal necrosis were extracted from the medical records.

Results—Twenty-nine patients with reports of SPS crystals were identified. Nine cases were excluded as incidental findings with normal mucosa. Nine patients were excluded as their symptoms began before SPS administration or because an alternate etiology for bowel ischemia was identified. Eleven patients had confirmed intestinal necrosis and a temporal relationship with SPS administration suggestive of SPS-induced necrosis. Only 2 patients were postoperative, and only 4 had end-stage renal disease (ESRD). All patients had documented hyperkalemia, received oral SPS, and developed symptoms of intestinal injury between 3 hours and 11 days after SPS administration. Four patients died.

Conclusion—Intestinal ischemia is a recognized risk of SPS in sorbitol. Our series highlights that patients may be susceptible even in the absence of ESRD, surgical intervention, or significant comorbidity.

Keywords

cation exchange resins; hyperkalemia; ischemic colitis; kidney failure

Sodium polystyrene sulfonate (SPS, Kayexalate) administered in sorbitol is a recognized, although infrequently reported, cause of intestinal necrosis. SPS, a cation-exchange resin, is given to patients with hyperkalemia as a means of binding and excreting potassium through the gastrointestinal tract. When administered orally, SPS releases sodium ions in the acidic

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stomach, binds hydrogen ions, and subsequently exchanges hydrogen for potassium in the small and large intestine.[1] Exchange resins were first synthesized in 1935, first described as a treatment in medical patients in 1961, and approved for use in the United States in 1975.[1,2] In its early use, SPS was administered as a suspension in water; however, concerns of constipation and fecal impaction led to the common practice of administering SPS with hypertonic sorbitol, a cathartic agent.[2] Sorbitol, rather than SPS resin itself, has been implicated in the development of intestinal injury.

Twenty-four cases of intestinal necrosis secondary to SPS in sorbitol have been reported to date, initially in the renal transplant literature.[1,3–14] The vast majority of these cases occurred postoperatively; in the critically ill, in patients with end-stage renal disease (ESRD), and in those with uremia. This entity has been infrequently described in less-ill and/or nonsurgical patients.

The goal of this study was to identify patients from our institution with probable SPS-induced intestinal necrosis in an effort to further describe their medical comorbidities, potential predisposing conditions, and clinical outcomes.

Methods

We conducted a retrospective chart review with the approval of the institutional review board and in compliance with the *Health Insurance Portability and Accountability Act* (*HIPAA*). The surgical pathology database at Rhode Island Hospital was searched to identify all specimens containing SPS crystals between December 1998 and June 2007. SPS crystals were identified based on their rhomboid, basophilic appearance, mosaic pattern, and adherence to surface epithelium (Fig.).[15] These reports were reviewed by an expert pathologist to identify cases of true mucosal injury and intestinal necrosis. Cases with normal mucosa, in which SPS crystals were an incidental finding, were excluded. Patients whose symptoms of intestinal ischemia developed prior to SPS administration were also excluded. Patients with potential alternate causes of intestinal ischemia (eg, infectious colitis or mesenteric ischemia) were excluded as the exact role of SPS-sorbitol in relation to these other factors could not be determined. Charts were then reviewed to ascertain patient demographics, medical comorbidities, hospital courses, and clinical outcomes for all patients with confirmed SPS-induced intestinal injury.

Results

Twenty-nine patients with reports of SPS crystals in surgical pathology specimens were identified. Of these, a total of 9 patients were excluded as incidental SPS crystals in a background of normal intestinal mucosa. Three patients were excluded as their symptoms of intestinal ischemia began prior to SPS administration (range: 3–14 days). An additional 6 patients had conditions which are known to cause intestinal ischemia and were therefore excluded from the analysis (Table 1).[16–19]

Of 29 patients, 11 were identified with confirmed intestinal ischemia and a temporal relationship with SPS-sorbitol administration that was suggestive of SPS-induced intestinal necrosis (Table 2). Histopathologic findings ranged from focal ulceration to transmural necrosis (Table 3). Only 2 patients were admitted for surgical procedures, both orthopaedic (knee replacement and hip fracture). The most common admission diagnoses were pneumonia and exacerbation of chronic obstructive pulmonary disease (COPD). Mean age was 70.8 (range: 30–91) with a female predominance (9/11 = 81.8%). Only 4 out of 11 patients (36%) had ESRD requiring hemodialysis. Three patients presented with hyper-kalemia despite normal renal function. The majority of patients had hypertension and

coronary artery disease. A minority had diabetes mellitus, hyperlipidemia, and COPD. The average potassium level was 6.4 mEq/L (range: 5.5– 8.3), treated with a mean SPS dose of 92 g (range: 30–170 g). Only 2 patients had symptoms of uremia and/or associated EKG changes. All patients received oral SPS. In 2 patients, the dosage of SPS was not recorded.

The most common symptoms indicating intestinal ischemia were abdominal pain (9 patients), distension (5 patients), and gastrointestinal bleeding (4 patients). Symptoms began between 3 hours to 11 days after SPS administration. Ischemia mainly affected the colon (10 patients) with 1 patient demonstrating isolated small bowel injury. Distribution in the colon was variable, including isolated right, left, and pancolonic involvement. Overall mortality in our series was 36%.

Discussion

Intestinal necrosis is a recognized complication of SPS administered in sorbitol, with significant morbidity and mortality. Incidence of SPS-mediated intestinal injury has been estimated as 0.27% to 1.8%.[3,7] Recognition of this entity at our institution prompted our retrospective investigation into clinical characteristics that affected patients might have in common. To our knowledge, our study involves the largest series of patients with intestinal necrosis suspected to be secondary to SPS in sorbitol. Review of our case series revealed several unexpected and unique findings.

First, the majority of our patients were admitted with medical diagnoses, with only 2 patients undergoing surgical procedures prior to SPS administration. This is in marked contrast to prior reports, which described this entity primarily in postoperative patients.[1,3–14] We also document that a minority of affected patients had end-stage renal disease (ESRD), again in contrast to prior reports. ESRD may predispose patients to intestinal necrosis through changes in blood volume during dialysis, hyperreninemia, elevated prostaglandin production, and localized colonic mesenteric vasospasm. [1,3,7] Renal transplant patients may be further susceptible due to chronic immunosuppressive therapy.[6,20] Likewise, delayed intestinal transit in postoperative patients, due to ileus or opiate use, slows SPS transit leading to increased risk of mucosal injury.[3] Our series highlights that patients need not have ESRD or significant surgical interventions to be susceptible to SPS-induced necrosis. Furthermore, the severity of illness in these patients at the time of admission was generally low. In particular, patients 2, 5, and 9 had few comorbidities, were admitted for noncritical illnesses, and expired as a result of intestinal injury. This suggests that non-postoperative patients and patients without significant vascular compromise are potentially at risk for this complication. Overall mortality was found to be 36% in our series, which is consistent with previous reports.[1,3–14]

Given the severity of intestinal complications, the therapeutic role of SPS needs to be re-evaluated. One gram of SPS possesses a theoretical in-vitro exchange capacity of 2 to 3.1 mEq of potassium and an *in vivo* capacity of approximately 1 mEq.[21] Early clinical studies demonstrated the potential of SPS resin to lower potassium; however, results may have been confounded by the patients' low potassium, high glucose diet, as well as the use of other potassium-lowering agents (insulin, bicarbonate).[22,23] Subsequent studies have questioned the effectiveness of SPS resin. *In vivo* potassium binding capacity may be lower than previously estimated, on the order of 0.4 to 0.8 mEq per gram of SPS.[24] Additionally, some of the potassium bound by SPS resin is likely already destined for excretion through the bowel. Further, cathartics used with SPS may produce a degree of extracellular volume contraction, acidosis, and may subsequently elevate serum potassium.[25] Gruy-Kapral et al[25] studied the effects of single-dose SPS resin on serum potassium levels and failed to

demonstrate a decrease below pretreatment values. Similar findings have been documented in neonates.[26]

Second, our series also highlights the questionable use of SPS resin in certain clinical circumstances. Several patients in our series received SPS despite normal renal function, when diuretics alone may have succeeded in lowering serum potassium levels. One such patient subsequently expired. Furthermore, patients with ESRD with intact hemodialysis access were given substantial doses of SPS resin, when dialysis would have offered definitive therapy. In cases where more rapid reduction is warranted, alternative means should be considered, such as intravenous calcium, insulin, bicarbonate, and inhaled beta-adrenergic agonists.[26] SPS resin has a slow onset of action, on the order of hours to days, contraindicating its use as sole therapy for life-threatening hyperkalemia.[27,28]

Finally, if SPS resin is utilized, the addition of sorbitol should be avoided. The role of sorbitol as the cause of mucosal injury has been previously outlined. Lillemoe et al compared the effects of SPS alone, SPS in sorbitol, and sorbitol alone in both uremic and nonuremic rats. Only those rats that received sorbitol (either alone or with SPS) developed histologic intestinal changes and associated morbidity. SPS alone did not cause intestinal injury.[4] It is believed that the hyperosmotic load of sorbitol may directly damage intestinal mucosa, cause vasospasm of the intestinal vasculature, and exacerbate inflammation through elevated prostaglandin levels.[11,12,29] The resulting histopathologic changes vary from patchy mucosal ulcerations to pseudomembranes and transmural necrosis, all findings characteristic of ischemic bowel, but with an absence of large vessel disease.[7,8,13] Given the preponderance of evidence implicating sorbitol in clinically significant intestinal necrosis, alternate vehicles for SPS should be considered. Proposed examples include water, syrup, milk, lactulose, and SPS brownies.[13,30]

Future studies are needed to determine the safety of SPS administered in alternative vehicles. Additionally, dosing studies may ascertain whether there exists a threshold of SPS-sorbitol administration above which intestinal injury is more likely to develop. The major limitation of our study is its retrospective, observational nature, as well as its small sample size. Additionally, excluding patients with a potential alternate etiology for intestinal ischemia may have underestimated the risk of SPS in our series. However, while SPS administration may have contributed to intestinal necrosis in these patients, the timeframe and presence of alternate conditions argues against a major role of SPS-sorbitol in these cases. Finally, without a control group we are unable to make conclusions regarding a positive association between SPS use and intestinal necrosis. Nevertheless, our case series demonstrates that patients without previously hypothesized risk factors may remain susceptible to this entity, a finding in contrast to prior investigations. Further studies are needed to examine the absolute strength of association between SPSsorbitol and intestinal ischemia.

Conclusion

SPS in sorbitol has been implicated in the development of intestinal necrosis, primarily mediated by the sorbitol component. Previous studies documented these findings almost exclusively in postoperative, renal transplant, and critically ill patients. Our study highlights that all patients are potentially susceptible, including those without previously described comorbidities. The indications for SPS resin use, as well as alternative vehicles for its delivery, should be re-evaluated. SPS-induced intestinal ischemia remains an under recognized, easily avoided complication, associated with significant morbidity and mortality. Physicians who routinely use this agent in sorbitol should be aware of its life-threatening complications.

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Key Points

- Intestinal ischemia is a recognized risk of sodium polystyrene sulfonate (SPS, Kayexalate) in sorbitol, with significant associated morbidity and mortality.
- Patients may be susceptible to intestinal injury even in the absence of previously hypothesized risk factors.
- When treating hyperkalemia, alternative means of potassium reduction should be considered.

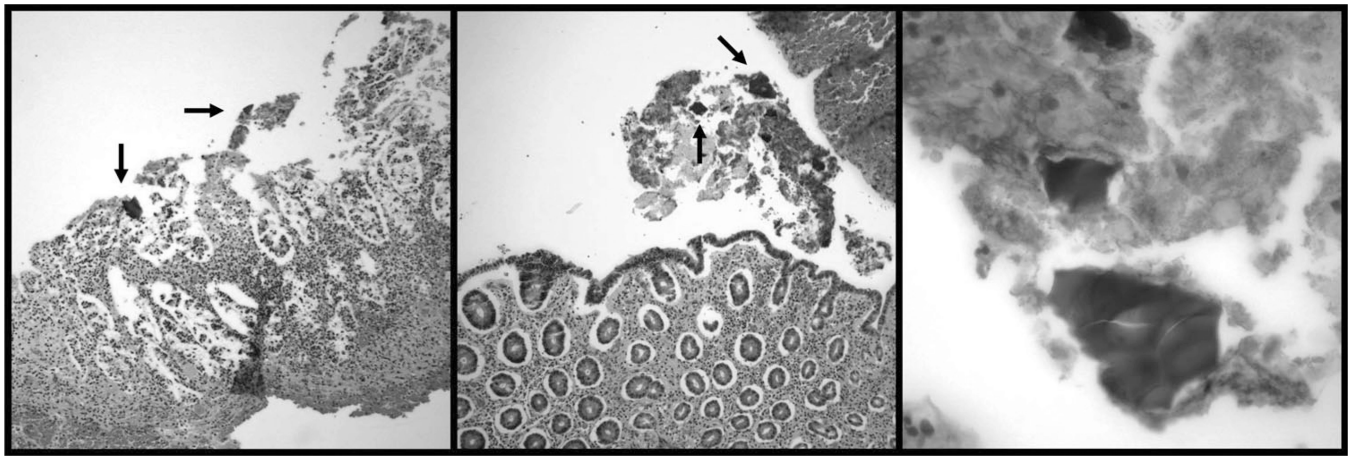

Fig.

Histopathological Findings. Left: Ischemic and necrotic epithelium with SPS crystals (arrows) (H&E orig. mag. ×20); Center: Ischemic mucosa with epithelial attenuation, atrophy, and SPS crystals (arrows) (H&E orig. mag. ×20); Right: SPS fragments (H&E orig. mag. ×60).

Table 1

Patients excluded due to alternate etiology[a]

Pt.	Age	Diagnosis	Course	Outcome	Pathology
1	65	*Clostridium difficile* colitis	Diarrhea, pancolitis, *C. difficile* toxin positive. SPS administered on admission	Total colectomy	Pseudomembranous colitis
2	58	Mesenteric ischemia	1 wk abdominal pain + rectal bleeding; SPS administered on admission	MRA confirmed IMA stenosis. Inferior mesenteric artery stented	Colonoscopy: mucosal fibrinoinflammatory exudates and mucosal necrosis
3	64	AAA repair/intra-operative hypotension	Intraoperative hypotension complicating AAA repair, dusky bowel noted; SPS administered postoperatively	Sigmoid resection postoperative day 1	Transmural necrosis
4	32	Bowel obstruction	Admitted with bowel obstruction, administered SPS at presentation	Hemicolectomy; intestinal ischemia secondary to obstruction	Mucosal transmural necrosis; omental fat necrosis with chronic inflammation
5	88	*C. difficile* colitis	1 wk of diarrhea, abdominal pain after antibiotics. Administered SPS on admission. Septic	Colonoscopy. Medically treated for *C. difficile* infection	Pseudomembranous colitis
6	73	Rectovaginal fistula	Rectal bleeding × 2 d, given SPS on admission	Sigmoid resection: rectovaginal fistula w/surrounding inflammation	Dense serosal adhesions, chronic transmural inflammation and focal transmural necrosis

[a]AAA, abdominal aortic aneurysm; SPS, sodium polystyrene sulfonate; MRA, magnetic resonance angiography; IMA, inferior mesenteric artery.

Table 2

Patient demographics, comorbidities, interventions, and outcomes[a]

Case	Age (yr), sex	Comorbidities	Admission diagnosis	Potassium (mEq/L)[b]	SPS dose (g)	Time to symptoms (d)[c]	Patient expired
1	62 M	ESRD, CAD, HTN	Rectal bleeding	7.3	170	<1	N
2	83 F	CAD, HTN, dyslipidemia, COPD	Chest pain	5.8	120	2	Y
3	63 F	CAD, HTN, DM2, dyslipidemia, hypothyroid, pancreatitis	Pancreatitis	6.5	120	1	N
4	78 F	CAD, HTN, ESRD, atrial fibrillation, hypothyroid	Pelvic fracture	6.5	60	<1	N
5	83 M	CAD, HTN, dyslipidemia, CHF, COPD	COPD	6.8	135	2	Y
6	75 F	CAD, HTN, dyslipidemia, DM2, CKD	Pneumonia	5.5	60	3	N
7	30 F	ESRD, lupus nephritis	Depression	8.3	90	<1	Y
8	91 F	HTN, CKD	Pneumonia	6.1	30	5	N
9	85 F	HTN, COPD	COPD	5.7	45	3	Y
10	59 F	HTN, CKD, gout, adrenal insufficiency	Knee replacement	5.9	N/A	11	N
11	70 F	ESRD, HTN, DM2	Rectal bleeding	N/A	N/A	N/A	N

[a]ESRD, end-stage renal disease; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; DM2, diabetes mellitus, type 2; COPD, chronic obstructive pulmonary disease; N/A, not available; HTN, hypertension; SPS, sodium polystyrene sulfonate.

[b]Serum potassium at time of SPS administration.

[c]Time to intestinal symptoms after first SPS dose.

Table 3

Histopathologic findings in affected patients

Case	Histopathologic findings	Intervention	Intestinal involvement
1	Colonic mucosa with mild acute inflammation, focal ulceration, and granulation tissue	Colonoscopy	Right colon, splenic flexure
2	Hemorrhagic and hyperemic mucosa with focal transmural necrosis and fibrinoinflammatory exudates	Colectomy	Pancolonic
3	Ulcerated mucosa with fibrinoinflammatory exudates and focal necrosis	Colonoscopy	Right colon
4	Mucosa with acute colitis and fibrinopurulent exudates	Colonoscopy	Sigmoid colon, rectum
5	Transmural necrosis, perforation, and acute and chronic serositis	Small bowel resection	Small bowel
6	Focal necrosis and necroinflammatory exudates	Colonoscopy	Right colon
7	Diffuse transmural necrosis	Colectomy	Pancolonic
8	Ulcerated colonic mucosa with reactive epithelial changes	Colonoscopy	Rectum
9	Mucosal necrosis with necroinflammatory exudates	Colonoscopy	Left colon
10	Segmental ischemic necrosis, focally transmural, with evidence of perforation. Supportive serositis	Colectomy	Small intestine; right and transverse colon
11	Necrotic mucosa and fibrinopurulent debris	Colonoscopy	Right colon