Should we be moving away from Kayexalate® (Sodium Polystyrene Sulfonate)?

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Preceptor: Joanie Tulloch, Emergency Medicine Rotation
May 2017

Learning Objectives

- Describe the evidence supporting efficacy of sodium polystyrene sulfonate
- List the safety concerns for sodium polystyrene sulfonate
- Describe an approach to deciding who should or should not be using sodium polystyrene sulfonate

Background

Hyperkalemia

- **Definition**: serum K^+ level $\geq$ 5.5 mmol/L
- **Severe**: $K^+ \geq 6.5$ mmol/L **or** $K^+ \geq 6$ mmol/L + ECG changes/sxs

Causes:

- Impaired renal excretion of K+
  - acute/chronic renal failure
- Drugs
  - ACEI/ARB
  - Aldosterone antagonists
  - NSAIDs

Complications:

- **Cardiac** conduction abnormalities
  - Ventricular fibrillation
  - Bradyarrhythmia
  - Sinus arrest
  - Asystole
- **Muscle** weakness or paralysis
- Death

Pharmacist's Letter: Vetassa (Patiromer) and Management of Hyperkalemia
Dynamed: Hyperkalemia [cited 2017 May]

Goals of Therapy

- Prevent mortality
- Prevent complications of hyperkalemia
- Normalize serum K^+ levels
- Prevent hypokalemia with treatment
- Minimize adverse drug reactions

Treatment Strategies

- Identify and remove cause (e.g. hypovolemia, drugs)
- Protect and stabilize myocardium against hyperkalemia (when there is ECG evidence of cardiotoxicity)
  - Calcium gluconate
- Shift K^+ intracellularly
  - Insulin and Glucose
  - β2-adrenergic agonists
- Remove K^+ from the body
  - Sodium Polystyrene Sulfonate
  - Loop diuretics
  - Dialysis

Sodium Polystrene Sulfonate (SPS)

- **Brand Names**: Kayexalate®, Solystat®
- **Indication**: Hyperkalemia
- **Mechanism**: cation-exchange resin
  - Exchanges Na+ ions for K+ ions in the intestine
- **Doses**: 15g PO 1-4x/day, 30-50g PR q6h
- **Costs**: $3 per 15g (powder), $10 per 15g (suspension)
- **SEs:**
  - GI: anorexia, constipation, diarrhea, nausea, vomiting
  - LYTES: ↓Ca, ↓ K, ↓ Mg, ↑Na
- **Pharmacokinetics**:
  - Onset: 2 – 24 hours
  - Absorption: None

Lexicomp Monograph: Sodium Polystyrene Sulfonate
Monograph: Kayexalate ®
J Hosp Med. 2011 Mar;6(3):136-40.
Annals of Pharmacotherapy2016, Vol. 50(6) 455–462

Approval of SPS

- Approved in 1958
  - For treatment of hyperkalemia
- Approved in Canada since 1961

J Am Soc Nephrol 21: 733–735, 2010.
Annals of Pharmacotherapy 2016, Vol. 50(6) 455–462

Efficacy – Scherr, et al. (1961)

Management of Hyperkalemia with a Cation-Exchange Resin

Lawrence Scherr, M.D.[†], David A. Ogden, M.D.[‡], Allen W. Mead, M.D., Norton Spritz, M.D.[§], and Albert L. Rubin, M.D.[¶]

N Engl J Med 1961; 264:115-119 | January 19, 1961 | DOI: 10.1056/NEJM196101192640303

P	(N = 32) acute or chronic renal disease with serum K+ between 4.2-9.2 mmol/L
I	20 to 60g PO SPS or 10-40g PR SPS (with no sorbitol) • All had potassium-restricted diets
C	• No restrictions on other hyperkalemic treatments (e.g. Insulin/glucose, sodium bicarbonate)
O	After 24 hrs, mean ↓ in serum K^+ • PO: 0.9 $\pm$ 0.1 mmol/L • PR: 0.8 mmol/L

N Engl J Med 264: 115-9, 1961.

Efficacy – Flinn, et al. (1961)

Treatment of the Oliguric Patient with a New Sodium-Exchange Resin and Sorbitol — A Preliminary Report

Robert B. Flinn, M.D.[†], John P. Merrill, M.D.[‡], and Walter R. Welzant, M.D.[§]

N Engl J Med 1961; 264:111-115 | January 19, 1961 | DOI: 10.1056/NEJM196101192640302

P	(N = 10) oliguric pts • serum K+ between 6-7.3 mmol/L • all pts received 500-700mL of fluid daily
I	Group 1: 5 - 15g SPS with 70% sorbitol QID x 5 days
	Group 2: 200 mL enema with 40g SPS and 25% sorbitol daily x 5 days
C	Group 3: 10-20mL of 70% sorbitol syrup orally q2h until a loose bowel movement was produced daily x 5 days
O	**Day 5**: mean serum K^+ - Group 1: 5.2 mmol/L, Group 3: 4.6 mmol/L "Serum K+ showed similar reductions with combo tx vs. sorbitol alone" **Authors' conclusion**: SPS with sorbitol was effective for treating hyperkalemia in oliguric patients

N Engl J Med 264: 111-5, 1961.

Efficacy – Mistry, et al. (2016)

Evaluation of Sodium Polystyrene Sulfonate Dosing Strategies in the Inpatient Management of Hyperkalemia

Mielen Mistry, BScPhm, ACPR[1,2], Amanda Shea, BSP, ACPR[3], Pierre Giguère, BPharm, MSc[3], and My-Linh Nguyen, BScPhm, ACPR[3]

Annals of Pharmacotherapy
2016, Vol. 50(6) 455–462

DOI: 10.1177/1060028016641427
aop.sagepub.com
SAGE

D	Retrospective Chart Review
P	(N = 118) Adults admitted to the Ottawa Hospital who had received any dose of SPS (Jan 1, 2010 – Mar 23, 2014) **Excluded**: • concomitant therapy for treatment of hyperkalemia (except loop diuretics) • received > 2L of IV fluids
I	• PO 15g, 30g, 60g SPS (no sorbitol)
C	• PR 30g SPS (no sorbitol)
O	**Primary**: Δ in serum K+ level **Secondary**: • Proportion remaining hyperkalemia • Proportion with post-dose hypokalemia

Results

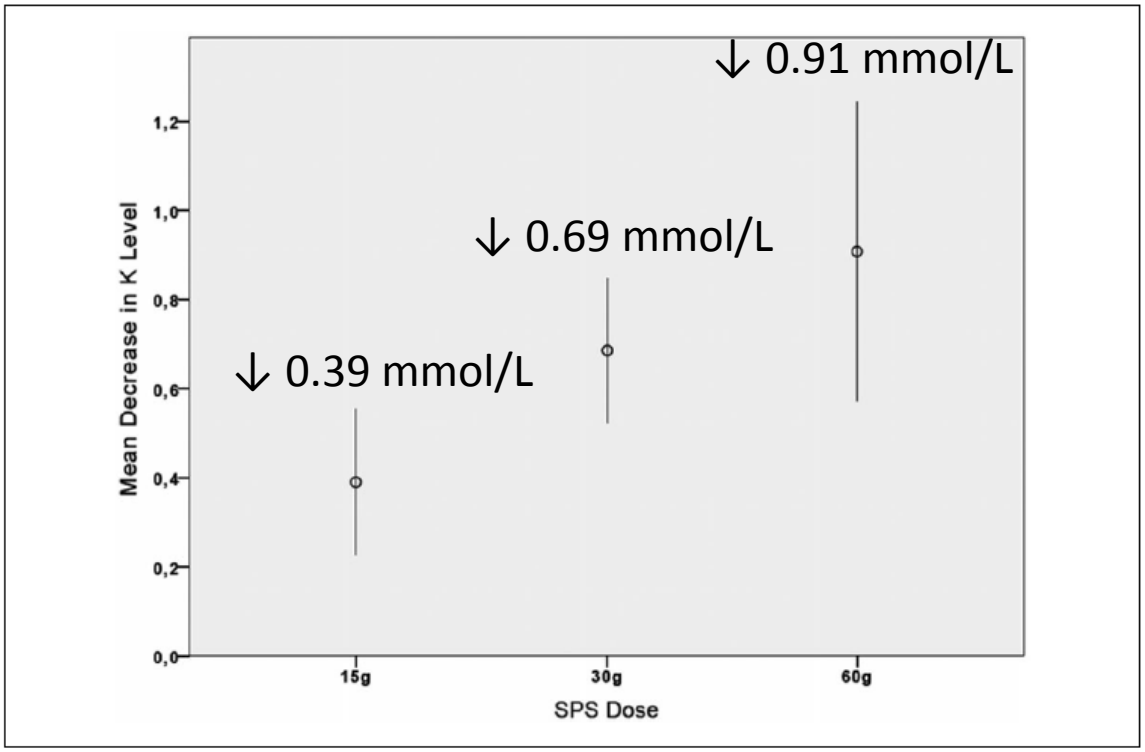


Figure 2. Sodium polystyrene sulfonate (SPS) dose-response.

PR 30g: ↓ 0.22 mmol/L

Efficacy:

- Dose-related ↓ in K+
- ↓ % of patients remaining hyperkalemic with ↑ doses
  - All patients receiving PR doses remained hyperkalemic

Safety:

- No patients experienced post-dose hypokalemia

Efficacy – Batterink, et al. (2015)

Effectiveness of Sodium Polystyrene Sulfonate for Short-Term Treatment of Hyperkalemia

Josh Batterink, Jane Lin, Sarah Hin Mui Au-Yeung, and Tara Cessford

D	Retrospective observational study
P	(N=138) Adults admitted to the internal medicine service of St Paul's Hospital (Jan 2011 – May 2012) • K+ level between 5.0 and 5.9 mmol/L during hospital stay **Exclusion**: chronic or acute renal failure, recent changes in medication (incl. Initiation/discontination of insulin/dextrose, high-dose SABA, loop diuretics) or diet that would affect serum K+ levels
I	(N = 66) Treatment with a dose of oral SPS (contains sorbitol)
C	(N = 72) No treatment
O	• Mean Δ in serum K+ (6-24 hrs after the index potassium measurement)

Can J Hosp Pharm. 2015;68(4):296-303

Doses in Treatment Group

N = 66

Doses	n (%)
10 g	1 (1.5)
15 g	32 (48)
30 g	31 (47)
45 g	1 (1.5)
60 g	1 (1.5)

Results

Efficacy:

- Δ in serum K+ (mmol/L, mean ± SD):

Treatment	Control	Difference	P-value
-0.58 ± 0.39	-0.44 ± 0.29	0.14	p = 0.036

SPS 15g	SPS 30g	Difference	P-value
-0.51 ± 0.38	-0.66 ± 0.40	0.15	p = 0.13

Safety:

- Screened for documented GI adverse events
  - 1 patient in treatment group had a documented nonfatal obstruction, unlikely related to SPS

Summary of Efficacy

- Efficacy with ↓ in serum K^+ levels
  - Supported by weak evidence
    - *Limitations*: non-randomized trials, small sample size, no control group, potential confounding factors
  - Lacking evidence on clinical outcomes
- K^+ reduction
  - ↓ 0.4 mmol/L^{15gPO} to 0.9 mmol/L ^{60gPO}
  - In mild hyperkalemia: difference of 0.14 mmol/L$^{vs.no\ tx}$
  - Questionable clinical significance
  - Suggests oral formulations are more efficacious than rectal

Safety

Formulations

- When SPS first came onto market...
  - Suspension in water
- Safety concerns:
  - Constipation
  - Life-threatening intestinal impaction
- Sorbitol added to ↓ these safety concerns and ↑ stool K^+ excretion

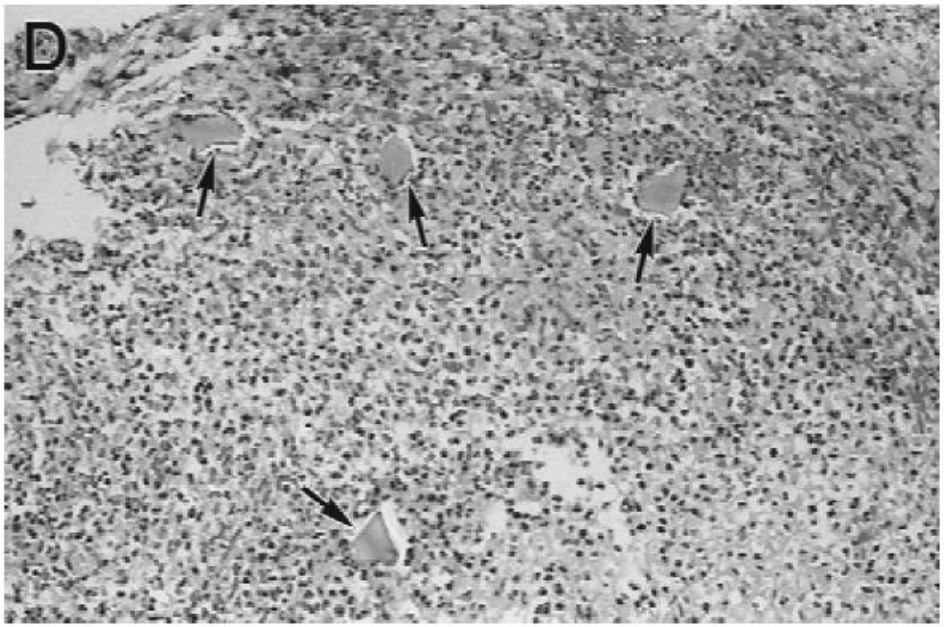
J Am Soc Nephrol 21: 733–735, 2010
Am J Surg Pathol 25(5): 637–644, 2001.
Gastroenterology 108: 752–760, 1995

FDA Warning

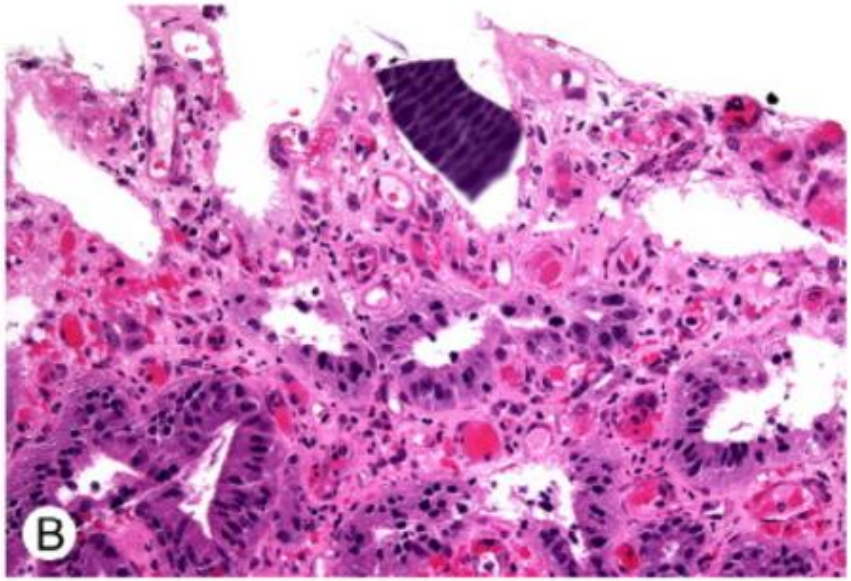
- **Intestinal Necrosis**:
  - Cases of intestinal necrosis...bleeding, ischemic colitis, perforation...have been reported in association with Kayexalate use
  - Majority of these cases reported the concomitant use of sorbitol
- Concomitant use of sorbitol is not recommended
  - Warning excludes pre-mixed suspension with 33% sorbitol

Is SPS blame-free?

- Proposed mechanism for SPS
  - Concretions of sodium polystyrene crystals adhere to mucosal surface ➔ direct injury



Multiple esophageal biopsies in this patient demonstrated only mucosal necrosis with Kayexalate crystals (arrows) in the inflammatory exudates.



Kayexalate injury (stomach)—erosive gastritis with angulated, basophilic crystal with mosaic pattern.

Am J Surg Pathol, Vol. 25, No. 5, 2001
Human Pathology (2007) 38, 527 – 536

Availability

- **Sodium Polystyrene Sulfonate**:
  - Powder (no sorbitol)
  - Suspension (23.5% sorbitol)

Kayexalate ® - Sanofi-aventis Canada monograph
Rexall – Prescription Drugs: Kayexalate [cited 2017 May 27]

Clinical Question

P I C O

P	Patients treated for hyperkalemia
I	Sodium Polystyrene Sulfonate
C	Placebo
O	Safety: • Intestinal necrosis • Gastrointestinal adverse events • Mortality

Search Strategy Results

Database	Pubmed, Embase
Search Terms	(sodium polystyrene sulfonate) OR (kayexalate) AND (gastrointestinal) OR (intestinal) OR (necrosis) OR (colon)
Limits	Humans, English, Available online
Results	• 1 Systematic Review • 6 Retrospective Studies • 2 Reviews • 31 Case Reports

CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

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

Ziv Harel, MD, MSc,[a,b] Shai Harel, MD, MS,[a] Prakesh S. Shah, MD, MSc,[c,d,e] Ron Wald, MDCM, MPH,[a,b] Jeffrey Perl, MD, SM,[a,b] Chaim M. Bell, MD, PhD[b,d,e]

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

Harel, et al. (2013)

Design	Systematic Review
Databases	• 1948 to July 2011 (MEDLINE), 1980 to July 2011 (EMBASE), Cochrane Central Register of Controlled Trials (1993 to July 2011) • Bibliographies of identified articles, websites of relevant drug agencies, professional associations in United States and Canada, Google scholar
Inclusion	• Case reports of gastrointestinal adverse events (i.e. unfavourable or harmful consequence involving the gastrointestinal tract) associated with SPS
Exclusion	• Patients < 18 years old • Patients with normal endoscopic/histologic findings upon investigation • Cases with a causality criteria of unlikely, conditional/unclassified, or unaccessable/unclassifiable according to the WHO causality assessment • Case-series with missing information that could not be obtained from authors
Results	**30 Reports** describing: • 58 cases (41 preparations with sorbitol, 17 without sorbitol)

Patient Characteristics

Demographics	
Age, years - mean ± SD	58 ± 17
Female, n (%)	29 (50)
Co-morbidities, n (%)	
Chronic Kidney Disease	15 (26)
ESRD requiring dialysis	26 (45)
Prior solid organ transplant	9 (16)
Current hospitalization, n (%)	
Post-operative	16 (28)
Acute kidney injury	12 (21)

Risk factors for GI AEs:

- 71% – history of kidney disease
- 9% – admitting diagnosis for renal transplantation
- 16% – history of solid organ transplant
- 28% – post-operative

SPS Treatment

Indication, n (%)	
Acute hyperkalemia	51 (88%)
# Doses, n (%)	
Single dose*	5 (9)
Multiple dose*	28 (48)
Chronic doses	7 (12)
Route	
Oral route	58 (77)
Rectal route	15 (20)
Nasogastric	2 (3)
Concomitant sorbitol	41 (71)

*A total of 33 cases reported single vs multiple doses

- Majority of cases:
  - Treatment of acute hyperkalemia
  - With concomitant sorbitol
  - By oral route
- # of doses
  - Not specified for 31% of cases
  - Most common: multiple dose
- Dose of SPS
  - Not specified in 34% of cases
  - Range: 15 g – 170 g
- Sorbitol concentration
  - 3 cases with 20% sorbitol
  - 1 case with 70% sorbitol

Results

Non-chronic doses: Time to symptoms (after 1st dose), in days, median (IQR)	2 (<1-5)
Presenting symptoms, n (%)	
Abdominal pain or tenderness	33 (57)
Nausea/vomiting	6 (11)
Blood per rectum	13 (24)
Diarrhea	10 (18)
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)

- Treatment of acute hyperkalemia
  - 50% of cases: within 24 hours to 5 days
- Presenting symptoms
  - Most common: abdominal pain or tenderness
- Location of injury
  - Most common: lower GI tract

Results, cont.

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)

- Histopathology of injury:
  - Most common:
    - Necrosis
    - Ulceration
  - SPS crystals commonly found in injured areas of GI tract
- Overall mortality rate: 33%
  - 94% of patients who died had colonic necrosis on biopsy

SPS with sorbitol vs. without sorbitol

	SPS + sorbitol (N = 41)	SPS - sorbitol (N = 17)	P-value
Single dose*	4 (10)	1 (6)	0.33
Chronic dose	0 (0)	7 (41)	<0.01
Time to sxs, median (IQR) days	1.5 (<1-3)	5 (<1-25)	0.27
Histopathology of injury, n (%)			
Necrosis	30 (73)	7 (41)	0.01
Ulceration	12 (29)	9 (53)	0.09
Perforation	3 (7)	2 (13)	0.62
SPS crystals	38 (93)	14 (82)	0.34
Outcome, n (%)			
Alive	22 (54)	11 (65)	0.43
Death	15 (36)	4 (24)	0.33
Not reported	4 (10)	2 (12)	1

- Use of SPS without sorbitol
  - More likely for chronic treatment of hyperkalemia
  - Wider IQR for time to symptoms for non-chronic doses
- Use of SPS with sorbitol
  - More likely to present with necrosis

Systematic Review's Conclusion

- "sodium polystyrene sulfonate use, with and without sorbitol, may be associated with fatal gastrointestinal injury"
- "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"
- "Until [rigourous assessment of optimal strategy, both in terms of safety and efficacy], physicians must be cognizant of the risk of these adverse events when prescribing sodium polystyrene sulfonate..."

Systematic Review Critique

STRENGTHS

- Search: extensive, multiple relevant databases
  - Published and unpublished
- Eligibility criteria: utilized WHO-UMC criteria for causality assessment
  - Included: certain, probable/likely and possible cases
- Compared SPS with and without sorbitol

LIMITATIONS

- Case reports and series
  - Missing information
  - Limited generalizability
- All cases
  - **Possible** causality: "Event with reasonable time relationship to drug intake; could also be explained by disease or other drugs"

Summary

- Suggests association of SPS with severe gastrointestinal adverse events
  - Majority of patients had risk factors for GI adverse events associated with SPS
- Cases reported with:
  - Single and **multiple** doses
  - **Acute** and chronic use
  - SPS **with** and without sorbitol
  - Upper and **lower** gastrointestinal injury

AJKD

Original Investigation

Association of Prescription of Oral Sodium Polystyrene Sulfonate With Sorbitol in an Inpatient Setting With Colonic Necrosis: A Retrospective Cohort Study

Maura A. Watson, DO, MPH,[1] Thomas P. Baker, MD,[2] Annie Nguyen, PharmD,[1] Mary E. Sebastianelli, RN,[3] Heather L. Stewart, MS,[2] David K. Oliver, RN,[1] Kevin C. Abbott, MD, MPH,[1] and Christina M. Yuan, MD[1]

Am J Kidney Dis. 2012;60(3):409-416.

Watson, et al. (2012)

D	Retrospective cohort study (Sept 1, 2001 – Oct 31, 2010) • Searched an anatomic pathology database for colonic tissue diagnoses and descriptions
P	Adults who received an outpatient or inpatient prescription at a tertiary medical center associated pharmacy
I	(N = 2,194 inpatients, N = 850 outpatients) SPS prescription
C	(N = 121,197) Prescription other than SPS
O	Tissue-confirmed diagnosis of colonic necrosis • considered SPS-associated if SPS was prescribed 30 or fewer days before tissue accession date

Results

- 98% – SPS with 33% sorbitol oral suspension
- Out-patient cases of colonic necrosis: Ø
- In-patient cases of colonic necrosis: 91

	SPS Rx	No SPS Rx
Colonic necrosis diagnosis	13	69
SPS within 30 days	3	

- **3 cases** with colonic necrosis associated with SPS
  - Median dose: 45 (30-60g/d)
- 9-year cumulative incidence **with SPS**: 0.14% (0.03-0.40)
- 9-year cumulative incidence **without SPS**: 0.065% (0.052-0.081)

Study's Conclusion

"Our results indicate that SPS-associated colonic necrosis risk is small and not significantly greater than background rate of colonic necrosis."

- NNH = 1,395 (95% CI: 298-5100)

Trial Critique

STRENGTHS

- Methodology:
  - Substantial duration of 9 years
  - Large cohort size
- Sub-group analysis
- Objective outcome assessment
  - Tissue biopsies

LIMITATIONS

- Retrospective design
  - Missing information (?dose, ?duration)
  - Confounding factors
  - ?Compliance of out-patients
- Limited generalizability
  - Single center
- Outcomes
  - Tissue biopsies
  - ?closer monitoring for in-patients (risk of detection bias)
  - Determination of association (prescription 30 days prior to biopsy)

Summary

- Sodium Polystyrene Sulfonate with 33% sorbitol associated with a low incidence of biopsy-confirmed colonic necrosis
  - 9-year cumulative incidence of: 0.14%
    ➔ 0.59% (incl. 10 cases with SPS Rx "not associated" with SPS)
  - Does not capture upper GI injury, ulcerations and other GI complications

dx.doi.org/10.1016/j.amjmed.2013.05.010

Health Canada
www.hc-sc.gc.ca

Canada Vigilance Adverse Reaction Database

- **Brand Name/Active Ingredient:** polystyrene sulfonate
- **Initial Received Date:** 1965-01-01 **to** 2016-12-31
- **Results**: 36 reports

Results – Gastrointestinal AEs

- **Reactions** (N = 36):
  - GI mucosal necrosis: 6 cases
  - Diarrhea, constipation, vomiting: 4 cases
  - Intestinal ischemia, perforation and crystal deposits: 1 case
  - Microscopic colitis: 1 case
  - GI tract irritation: 1 case
- **Doses**: 15 – 50 g

Summary

Goals of Therapy	Evidence
EFFICACY	
Mortality associated with hyperkalemia	✘ Not shown to prevent mortality or complications of hyperkalemia
Clinical complications	
↓ serum K+ levels	↓ 0.4 mmol/L$^{15g\ PO}$ to 0.9 mmol/L$^{60g\ PO}$ • SS difference of 0.14 mmol/L$^{15\text{-}30gPO\ vs.no\ tx}$
SAFETY	
Drug-induced hypokalemia	Low risk of hypokalemia
Gastrointestinal Adverse Events	Low risk of severe GI adverse events • risks appear to be higher with combination with sorbitol • unclear if risks higher due to higher use of combination *Lexicomp Monograph*: <1%, gastrointestinal hemorrhage, gastrointestinal ulcer, intestinal necrosis, intestinal perforation, ischemic colitis • Limited evidence with long-term use of SPS
Mortality associated with SPS	Low risk of mortality associated with SPS

Who should we not be using SPS in?

Risk Factors for serious GI AEs

- Reduced GI motility
  - Drugs (e.g. Opiates)
- ✗ Any post-operative patients *until* resumption of normal bowel function
- ✗ Obstructive bowel disease
- ✗ Ileus
- Underlying bowel disease (e.g. ulcerative colitis)
- ✗ At risk for developing constipation or impaction
- Renal transplant patients
- Renal insufficiency/failure
  - Possible mechanism: ↑ renin levels predispose pt to non-occlusive mesenteric ischemia via angiotensin-mediated vasoconstriction
- Solid organ transplant
  - Especially patients with recent history
- Hypovolemia
- Critically ill or sepsis

✗ Contraindications

J Trauma. 2001;51:395–397.

Uptodate: treatment and prevention of hyperkalemia in adults

Management of Hyperkalemia

If ECG Δs associated with hyperkalemia:

- Calcium gluconate 1g IV

For potassium shift into cells:

- Insulin regular 10units IV + Dextrose 50% 25g (50mL) ↓0.5-1.2meq/L
- Nebulized or inhaled salbutamol ↓0.5-1.5meq/L

For potassium removal:

- Loop diuretics (Furosemide 20-40mg IV)
- Sodium Polystyrene Sulfonate
  - Consider spacing oral medications by at least 6 hours apart
  - Monitor: abdominal pain/tenderness, nausea/vomiting, diarrhea, blood per rectum
- Dialysis

Uptodate: Treatment and prevention of hyperkalemia in adults

How about Calcium Polystyrene Sulfonate?

- **Brand Name**: Calcium Resonium®
- **Formulations**: Powder for suspension (no sorbitol)
- **Safety**:
  - *Lexicomp monograph*: <1%, Bezoar formation, fecal impaction, GI necrosis, GI obstruction, GI ulcer, ischemic colitis, mesenteric ischemia, rectal, hemorrhage, intestinal stenosis
  - Several case reports suggesting association between calcium polystyrene sulfonate, alone and serious gastrointestinal AEs such as colonic necrosis[1,2,3,4]
- Similar pre-cautions and contraindications
- **Costs**: $6 per 15 g dose

[1]J Korean Med Sci 2009;24:1207-11.
[2]Rev Esp Enferm Dig 2013; 105(4):232-234.
[3]J Formos Med Assoc (2015) 114, 1008-1010
[4]Ann Pharmacother 2011;45:e13.
Resonium Calcium® - Sanfo-aventis Canada monograph
Uptodate: Calcium Polystyrene Sulfonate Monograph