

The Use of Sodium Polystyrene Sulfonate in the Inpatient Management of Hyperkalemia

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Background: Limited data exist on the precise dose of sodium polystyrene sulfonate (SPS) needed for specific potassium concentrations in the management of mild to moderate hyperkalemia in an inpatient hospital setting.

Methods: A retrospective cohort study involving a review of electronic medical records of inpatients receiving SPS for the treatment of hyperkalemia was conducted at the Jesse Brown Veteran Affairs Medical Center, between January 1, 2006 and December 31, 2006. Hyperkalemia was defined as a serum potassium concentration >5.1 mmol/L. The primary endpoint was the mean change in potassium concentration associated with specific SPS dosage administration.

Results: A total of 122 patients were selected for inclusion in the analysis. The mean potassium concentrations before SPS administration were 5.40 ± 0.18 mmol/L, 5.51 ± 0.30 , 5.83 ± 0.46 , and 5.92 ± 0.30 in the 15, 30, 45, and 60 gm groups, respectively. The mean potassium concentration decreased by 0.82 ± 0.48 mmol/L in the 15 gm group, 0.95 ± 0.47 in the 30 gm group, 1.11 ± 0.58 in the 45 gm group, and 1.40 ± 0.42 in the 60 gm group. After a single dose of SPS, the mean potassium concentration was within normal range in 115 patients (94%).

Conclusions: A possible direct dose response relationship between SPS and the reduction in serum potassium concentration was found and should be evaluated prospectively. *Journal of Hospital Medicine* 2011;6:136–140.

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Hyperkalemia is a common and potentially life-threatening problem encountered in many clinical settings. The incidence of hyperkalemia in hospitalized patients has been estimated to be between 1% and 10% in the United States each year.^{1–6} Medications are thought to contribute to the development of hyperkalemia in 35% to 75% of hospitalized patients.^{1–2,9} Medications known to cause hyperkalemia include angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists (ARBs), potassium-sparing diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), potassium supplements, and antibiotics such as trimethoprim/sulfamethoxazole. Patients with hyperkalemia may develop neuromuscular symptoms such as fatigue, muscle weakness, tingling, numbness, and cramping. The most deleterious effect of hyperkalemia is cardiac toxicity, including life-threatening arrhythmias.^{3,7–11}

Sodium polystyrene sulfonate (SPS) or Kayexalate is a cation-exchange resin that is commonly employed to lower total body potassium in patients with mild to moderate hyperkalemia.^{12–14} It removes potassium from the gut in exchange for sodium. SPS can be given orally or as an enema. When given

orally, it is commonly administered with sorbitol to promote diarrhea. The onset of action is within 1 to 2 hours and lasts approximately 4 to 6 hours. The recommended average daily dose is 15 gm to 60 gm given as a single dose or in divided doses. An in vitro study indicated that each gram of resin binds to approximately 3.1 mEq of potassium.¹⁴ However, the majority of the exchange capacity is utilized for cations other than potassium. Therefore, the in vivo exchange capacity is thought to be no greater than 1 mEq of potassium per gram of resin.

There are conflicting data regarding the effectiveness of exchange resins.^{1,13} In 1998, Guy-Kapral et al.¹⁵ found that a 30-gm dose of SPS failed to lower serum potassium concentration in end-stage renal disease patients who were normokalemic. In contrast, Flinn et al.¹⁶ demonstrated effective lowering of serum potassium over a period of several days in which repeated doses of SPS were given to hyperkalemic patients. Moreover, in another study, serum potassium concentration was reduced by 1.0 mEq/L in 24 hours.¹⁷ However, this study was limited since subjects also received other potassium-lowering agents such as insulin/glucose or sodium bicarbonate.

In 2004, Mikrut and Brockmiller-Sell¹⁸ studied the dose response between SPS and serum potassium concentration. Their data demonstrated an average reduction in potassium concentration of approximately 1 mmol/L and 1.48 mmol/L following a 30 gm and a 60 gm dose of SPS, respectively. However, the study was small ($n = 39$) and only evaluated 2 dosages. In clinical practice, there is wide variability in SPS dosing. Furthermore, studies assessing the effects of different doses of SPS are lacking. Often, the dose chosen is dependent on comorbid conditions, concomitant medications and provider experience in treating hyperkalemia. The aim of our study was to examine the single-dose effect of SPS on potassium concentration in hospitalized, hyperkalemic patients and to compare the potassium lowering effects of SPS doses commonly used.

Methods

Study Population

A retrospective cohort study involving a review of electronic medical records of inpatients receiving SPS for the treatment of hyperkalemia was conducted at the Jesse Brown Veteran Affairs Medical Center, between January 1, 2006 and December 31, 2006. Hyperkalemia was defined as a serum potassium concentration >5.1 mmol/L, as this concentration corresponded to the upper limit of normal for serum potassium at our hospital. The patient list was generated from prescription databases. Exclusion criteria included: chronic SPS use, rectal administration of SPS, multiple doses of SPS spaced less than 6 hours apart, a hemolyzed laboratory specimen, current hemodialysis, lack of a follow-up serum potassium concentration, or other treatments started for hyperkalemia at the time of the event, specifically insulin, dextrose, albuterol, and/or furosemide. This study protocol received approval from the local Institutional Review Board and the hospital's research and development committee.

Data Collection

The Computerized Patient Record System (CPRS), the electronic medical record system used at Jesse Brown VA Medical Center (JBVAMC), was utilized to gather patient baseline demographic information consisting of age, gender, weight, and height. Data on comorbid conditions such as hypertension (HTN), diabetes mellitus (DM), chronic heart failure (CHF), chronic kidney disease (CKD), and acute renal failure (ARF) was identified from the patient's problem list in the medical record. Additionally, the authors abstracted information about concomitant hyperkalemia-precipitating medications including ACE inhibitors, ARBs, potassium-sparing diuretics, aldosterone antagonists, NSAIDs, potassium supplements, and antibiotics such as trimethoprim/sulfamethoxazole. Progress notes and discharge summaries were reviewed for documentation of ARF. Laboratory information including serum creatinine, blood urea nitrogen, potassium, sodium, and calcium concentrations before and after SPS

administration was recorded. The date and time of laboratory draws were also collected. Data on SPS administration regarding time and date, as well as dosing information, was obtained from the medication administration records.

Outcomes

The primary outcome were the mean change in serum potassium after a single dose of SPS compared to the baseline. The data were also evaluated based on the dose of SPS that was administered, 15 gm, 30 gm, 45 gm, or 60 gm doses of SPS. Secondary outcomes were the mean change in sodium and calcium concentrations.

Statistical Analysis

In order to complete the statistical analysis for the study, continuous variables were summarized as mean \pm standard deviation, and categorical variables were summarized as frequency counts and proportions. Group comparisons for categorical data in baseline characteristics were performed using the Fisher's exact test and the chi-square test. The comparisons for continuous data in baseline characteristics were performed using analysis of variance (ANOVA). A paired *t*-test was then used to compare changes in potassium, calcium, and sodium concentrations and again to compare the changes in potassium concentrations by different dosage groups. Subset analysis also required the paired *t*-test. The differences in the change of potassium concentration between dosage groups were analyzed by ANOVA. Post hoc comparisons were performed to identify which groups were statistically different from each other. A *P* value less than 0.05 was considered statistically significant. The effect of dosage on primary outcome was also assessed by adjusting baseline characteristics using analysis of covariance (ANCOVA). Least square means (LSMEAN) of the primary outcome were calculated using the ANCOVA model with the SPS dosage groups as the main categorical independent variable and the baseline characteristics in Table 1 as the covariates. The LSMEAN are group means after controlling for covariates (they are the predicted group means, predicted as the population mean values of the covariates in the model). All statistical analyses were done using SAS software, version 9.1 (Cary, NC).

Results

Patient Characteristics

Study subjects consisted of patients who received SPS in the hospital for treatment of hyperkalemia. A total of 140 patients were identified and 122 met the inclusion criteria. Eighteen patients were excluded for current hemodialysis, receiving other treatments for hyperkalemia, and specimen hemolysis. Of those who were included in the study analysis, 30 patients received 15 gm of SPS, 60 patients received 30 gm, 19 patients received 45 gm, and 13 patients received 60 gm. Baseline characteristics of included patients are shown in Table 1. The majority of patients were male (99%) and had comorbid conditions.

TABLE 1. Patient Baseline Characteristics

	All (n = 122)	15 gm (n = 30)	30 gm (n = 60)	45 gm (n = 19)	60 gm (n = 13)	P Value
Male, n (%)	121 (99)	30 (100)	60 (100)	18 (95)	13 (100)	0.14
Age (year)	69.0 ± 11.4	70.71 ± 0.5	70.2 ± 11.5	68.0 ± 1.7	63.8 ± 12.2	0.25
Height (inch)	69.0 ± 3.5	69.2 ± 4.6	68.8 ± 3.3	68.2 ± 3.0	70.5 ± 1.3	0.31
Weight (kg)	81.4 ± 20.7	77.3 ± 15.0	83.1 ± 23.3	82.7 ± 21.7	81.6 ± 18.1	0.64
Hypertension, n (%)	96 (79)	29*(97)	47 (78)	12 (63)	8 (62)	0.01*
Diabetes Mellitus, n (%)	41 (34)	10 (33)	21 (35)	6 (32)	4 (31)	0.99
Chronic kidney disease, n (%)	46 (38)	10 (33)	21 (35)	8 (42)	7 (54)	0.57
Heart failure, n (%)	32 (26)	12 (40)	13 (22)	6 (32)	1 (8)	0.10
Serum creatinine (mg/dL)	2.57 ± 2.4	2.09 ± 1.5	2.93 ± 3.0	2.37 ± 1.2	2.29 ± 2.1	0.41
Acute renal failure, n (%)	84 (69)	19 (63)	45 (75)	12 (63)	8 (62)	0.55
Concomitant hyperkalemia-precipitating medications, n (%)	60 (49)	19 (63)	23 (38)	10 (53)	8 (61)	0.11

NOTE: The values in parenthesis are the percentages for the dichotomous variables and the standard deviations for the continuous variables are in the ± format.

* Statistically significant result.

TABLE 2. Summary of Changes in Electrolytes

Electrolytes	Pre-SPS	Post-SPS	Mean Change	P Value
K+(mmol/L)	5.57 ± 0.35	4.59 ± 0.46	-0.99 ± 0.51	<0.0001
Ca2+(mg/dL)	8.54 ± 0.81	8.46 ± 0.64	-0.07 ± 0.53	0.13
Na+(mmol/L)	136.7 ± 4.66	137.6 ± 4.65	0.89 ± 3.33	0.004

Abbreviation: SPS, sodium polystyrene sulfonate.

At baseline, the mean serum creatinine concentration was 2.57 ± 2.36 mg/dL. Documented acute renal dysfunction was present at the time of the hyperkalemic event in 69% of patients. Forty-nine percent of patients were taking at least one medication that can precipitate hyperkalemia. The most common medications were ACE inhibitors (52%). All baseline characteristics were similar among the different cohorts except for HTN. There were significantly more patients with HTN in the 15 gm dosage group compared to the others. There was no effect of baseline characteristics on the primary or secondary outcomes.

Clinical Outcome

A total of 115 patients (94%) achieved normalization of potassium concentration with a single dose of SPS. The mean SPS dose given was 31.84 ± 13.58 gm. The changes in mean electrolyte values for all patients are shown in Table 2. The mean reduction in potassium concentration was 0.99 ± 0.51 mmol/L (P < 0.0001). The follow-up potassium concentration was obtained on an average of 10 hours after administration of SPS. The mean reduction in calcium concentration was 0.07 ± 0.53 mg/dL (P = 0.13). Further, the mean reduction in sodium concentration was 0.09 ± 3.33 mg/dL (P = 0.004). Figure 1 depicts the change in serum potassium concentration in each of the SPS dosage groups. The mean change in potassium concentrations compared to baseline was statistically significant in all dosage groups. The mean reduction in potassium concentration achieved statistical

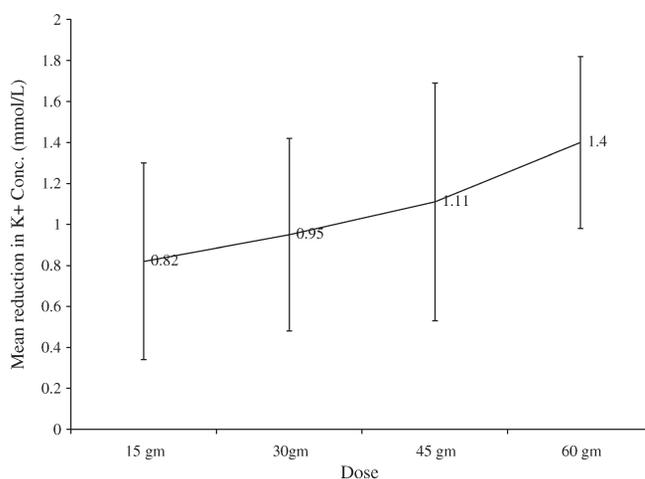


FIGURE 1. Mean Reduction in Potassium Concentrations. A trend test for testing dose–response relationship has a P value of 0.0003. The trend test regress mean reduction (the outcome variable) on the single ordinal variable created using the dosage level (ie, a linear regression of mean reduction on the ordinal dosage level, adjusted by the baseline variables in Table 1). The P value for the main regressor—the ordinal dosage level—has a P value of 0.0003, a strong evidence for the presence of trend.

significance between the 15 gm and 60 gm groups (P < 0.05) and between the 30 gm and 60 gm groups (P < 0.05) (Table 3). To adjust for the potential covariate effects in these group mean comparisons, we further calculated the LSMEAN. Table 3 presents the least square mean changes in serum potassium concentration in each of the SPS dosage groups. As shown in Table 4, the least square mean changes in potassium concentrations compared to the baseline were also statistically significant in all dosage groups. These group differences remain significant, even after the adjustment by the baseline variables.

Subset Analysis

To address cointervention bias, an analysis of patients who were on at least 1 medication that predisposed them to

TABLE 3. Group Comparisons for Least Square Means of Potassium Reduction for the Dose Effect

Dose (gm)	Difference Between Means	CI for Difference Between Means
15-30	-0.13	-0.43, 0.16
15-45	-0.27	-0.66, 0.11
15-60*	-0.64	-1.09, -0.19
30-45	-0.14	-0.48, 0.20
30-60*	-0.50	-0.91, -0.10
45-60	-0.36	-0.82, 0.10

NOTE: Least square means (LSMEAN) are calculated using an ANCOVA model with Potassium Reduction as the outcome, the SPS dosage groups as the main categorical independent variable and the baseline characteristics in Table 1 as the covariates. The least square means are group means after having controlled for covariates (that is, they are the predicted group means, predicted at the population mean values of the covariates in the model). Tukey's method for multiple comparisons is used to adjust confidence limits for the differences of LS-means.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval.

*Statistically significant results.

TABLE 4. Least Square Means (LSMEAN) of Potassium Reduction, After Adjustment by the Baseline Variables in Table 1

SPS Dose	LSMEAN of Potassium Reduction	95% Confidence Limits	
15 gm	0.676566	0.119091	1.234041
30 gm	0.808860	0.260418	1.357302
45 gm	0.951205	0.431039	1.471371
60 gm	1.313806	0.718793	1.908818

NOTE: Least square means (LSMEAN) are calculated using an ANCOVA model with potassium reduction as the outcome, the SPS dosage groups as the main categorical independent variable and the baseline characteristics in Table 1 as the covariates. The least square means are group means after having controlled for covariates (that is, they are the predicted group means, predicted at the population mean values of the covariates in the model).

Abbreviations: ANCOVA, analysis of covariance; SPS, sodium polystyrene sulfonate.

hyperkalemia such as ACE inhibitors, ARBs, potassium sparing diuretics, aldosterone antagonists, NSAIDs, potassium supplements, and antibiotics such as trimethoprim/sulfamethoxazole ($n = 60$) were reviewed. Of the 60 patients, 30 received SPS and had hyperkalemia-precipitating medications adjusted and 29 patients received SPS alone. Of those who had medications adjusted, the majority of them (83%) had these medications discontinued. The mean potassium concentration before the intervention was approximately 5.6 mmol/L in both groups. The mean SPS dose given was also similar as well as the mean potassium reduction of approximately 1 mmol/L.

Discussion

In this study, we retrospectively examined inpatients who received a single dose of SPS for the treatment of hyperkalemia. In addition, we established a possible dose response relationship in the treatment of mild to moderate hyperkalemia with SPS monotherapy. Our data revealed that 94% of patients achieved normalization of serum potassium con-

centration with a single dose of SPS. None of the patients experienced hypokalemia as a result of SPS administration. Moreover, when compared to the work by Mikrut and Brockmiller-Sell,¹⁸ we found a similar reduction in serum potassium associated with the 30 gm (0.95 mmol/L vs. 1 mmol/L) and 60 gm (1.40 vs. 1.48 mEq/L) doses of SPS.

As expected, patients with higher serum potassium concentrations received higher SPS doses. Our data illustrated a possible direct, dose-response relationship between the SPS dose and the reduction in serum potassium concentration. All of the dosage groups produced a statistically significant reduction in potassium concentrations compared to baseline. Moreover, a statistically significant difference was found in the 60 gm group when compared to the 15 gm and 30 gm groups. The mean increase change in sodium of 0.89 ± 3.33 mmol/L was found to be statistically significant ($P = 0.004$) but not felt to be clinically relevant. The mean change in calcium concentration of -0.07 ± 0.53 was not statistically significant ($P = 0.13$).

As with any retrospective chart review, incomplete documentation limits data collection. This may have led to an underestimation of the presence of ARF or other risk factors for hyperkalemia at the time of the event. We excluded patients who received other treatment for hyperkalemia in order to truly assess the effects of SPS on potassium concentration. However, we did not account for all potential confounding variables that are likely to affect potassium concentration such as acid-base status and glycemic control at the time of the hyperkalemic episode. Also, dietary intake of potassium was not ascertained. Absence of a control group is also a limitation of the study, as it does not allow for complete causality to be established. The sample size, although significantly larger than previous studies, was small especially in regards to the subset analysis. Results cannot be generalized to women since the sample of females was very small or to those who were excluded from the analysis by design. Finally, this study evaluated hospitalized patients and direct extrapolation of the results to outpatient settings should be done cautiously, particularly in light of nutritional considerations.

Our study demonstrates a possible dose-response relationship in lowering potassium concentrations with SPS. The data presented in this paper can be used to develop a potential dosing guideline for the use of SPS in the clinical management of hyperkalemia in a variety of clinical settings. It provides a basis for a much needed prospective study to finalize a dosing scheme for the use of SPS. Having a dosing scheme would serve as a resource for determining what dose of SPS to give for varying degrees of hyperkalemia while being mindful that individual responses to potassium lowering effect of SPS might be variable.

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