Editorial

Damned If You Do, Damned If You Don't: Potassium Binding Resins in Hyperkalemia

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Sodium polystyrene sulfonate (SPS) potassium binding resins increase colonic potassium excretion and are approved by the U.S. Food and Drug Administration (FDA) for the treatment of hyperkalemia. In 2009, the FDA recommended that sorbitol, a cathartic often given with SPS to prevent obstipation, not be added to SPS powder because of associated colonic necrosis. A premixed oral suspension of SPS in 33% sorbitol was not included in this warning. SPS resins increase stool potassium excretion in normokalemic subjects, but proportionately more potassium is excreted due to cathartics when the two are combined. In hyperkalemic patients, oral SPS mixed in water significantly decreases serum potassium within 24 hours. SPS/sorbitol-associated colonic necrosis is most commonly seen in patients who have received enemas in the setting of recent abdominal surgery, bowel injury, or intestinal dysfunction. It is a rare event, on the order of 0.2 to 0.3%, almost exclusively present in patients at risk. The agent most likely associated with colonic necrosis is 70% sorbitol, and animal data support that etiology. There is very little data to suggest that oral SPS given with 33% sorbitol (in the premixed form) or SPS powder in water orally or as an enema causes colonic necrosis. SPS ion-exchange resins are the only agents, other than dialysis and diuretics, available to increase potassium excretion in hyperkalemia, and when used appropriately, they appear to be clinically effective and reasonably safe.

Sodium polystyrene sulfonate (SPS) potassium binding resins (Kayexalate, Kionex, and others) with and without an associated cathartic (usually sorbitol) have been in use for over 50 years and are FDA-approved for the treatment of hyperkalemia. In September 2009, the FDA recommended against the "concomitant use of sorbitol" with Kayexalate powder because of associated cases of colonic necrosis and other severe gastrointestinal side effects (1). However, this warning did not apply to premixed SPS in 33% sorbitol for oral use (various manufacturers), the only SPS resin available in many hospitals.

Sterns *et al.*, in a recent editorial review, concluded that SPS resins are "largely unproven and potentially harmful," especially when administered with sorbitol, and that clinicians should "exhaust other alternatives" (2). We feel these conclusions are immoderate. When indicated, and in patients who have no contraindication to their use, SPS resins are effective and reasonably safe. What is the "therapeutic niche" for SPS? What are the "alternatives", and what are their risks and benefits? Is SPS effective? What is the incidence of and risk factors for serious side effects?

Hyperkalemia may be an immediately life-threatening condition (3,4). Severe hyperkalemia can cause ventricular fibrillation or asystole, unless extracellular potassium is reduced (3–5). In one study of hospitalized hyperkalemic patients, mortality directly due to hyperkalemia was 1.7%, but overall mortality was 14% (6). Even relatively mild (5.5 to 6.0 mEq/L) hyperkalemia is associated with an increased risk of mortality within the next 24 hours, even without electrocardiogram (ECG) changes (7). Because of these associations, clinicians feel compelled to respond vigorously to hyperkalemia. Many of the agents we use for the treatment of acute hyperkalemia are unproven, as we would now require proof—but the majority clinical consensus is that they do work (3–5).

The first step of hyperkalemia management is to decide whether it is life-threatening—using ECG changes and the degree and rate of potassium elevation. If ECG changes exist, or potassium is very high, immediate treatment is begun with calcium gluconate, insulin, and dextrose, and inhaled beta agonists (3–5). Although effective, their action is temporary—lasting at most hours. They protect the neuromuscular membrane against hyperkalemia (calcium gluconate) or shift extracellular potassium into the intracellular space. Unless the rise in potassium was due to a cellular shift, excess potassium must subsequently be excreted (diuretics or SPS) or removed (dialysis). SPS may be used as "bridge" therapy while hemodialysis is arranged. If there are no ECG changes, and potassium elevation is moderate, excretion can be increased using SPS or diuretics, and the source of excess potassium (either by way of the diet or inhibition of excretion) corrected. Because the effects of SPS are delayed for at least 2 hours (peaking at 4 to 6 hours) (4,8), it is

not useful for acute potassium control. The only other "excretory" modalities available are dialysis and loop diuretics, both of which have limitations and potential side effects, and like SPS, may take hours to have an effect. Kaliuresis induced by loop diuretics (which have not, *per se*, been studied for the treatment of hyperkalemia) requires adequate kidney function, which is often not present (4,9), and at high doses may cause azotemia and ototoxicity (in up to 6 to 7% of patients, but usually reversible) (10). Hemodialysis, which may not be easily or quickly available, is expensive and resource-intensive and requires central venous access. Other treatments for hyperkalemia should never be withheld or delayed while waiting to start hemodialysis (3,4). Aside from loop diuretics and hemodialysis, there are no other alternatives to SPS.

When SPS resins were first introduced, dialysis was an infrequent procedure, and loop diuretics were in development. There was a clinical need for an agent that increased potassium excretion in oliguric kidney failure. It was known that patients could recover from acute kidney failure if they did not die of hyperkalemia, acidosis, uremia, or volume overload in the interim (11). This was the setting in which Scherr *et al.* (12) reported the efficacy of SPS in 1961. Thirty-two hyperkalemic patients were evaluated. Twenty-two patients received SPS (median dose 40 g/d; range 20 to 60 g) orally in water for a median of 3 days (range 1 to 6 days). Sixteen had either presumed acute tubular necrosis or acute glomerulonephritis and were oliguric. Six had chronic kidney disease. Blood urea nitrogen ($n = 15$) was 134 ± 17 mg/dl. Patients served as their own controls. It would have been unethical to treat patients with a placebo. Potassium before treatment was 6.4 ± 0.2 mEq/L. It declined significantly at the conclusion of treatment by 1.8 mEq/L (95% CI 1.3 to 2.4, $P < 0.0001$, paired t test), with a 0.9 ± 0.1 mEq/L ($P < 0.0001$, sign test) decrease within the first 24 hours. ECG changes correlated with the measured potassium decline. The only supplemental agents used were sodium bicarbonate (three patients) and 600 ml of 20% dextrose, given intravenously to the oliguric patients. All received a high-calorie, low-potassium diet. The hypertonic glucose may have lowered serum potassium, but supplemental insulin administration is not reported, and patients were not fasting, so the effect was likely not consistent (4).

Eight additional patients received SPS retention enemas in water (median dose 70 g; range 10 to 160 g). Two of these had tissue necrosis with rapidly rising potassium and SPS was ineffective, as would be expected, where prolonged dialysis is often required. Although potassium declined by 0.7 ± 0.3 mEq/L after the first 24 hours, there was no significant decrease in potassium at the conclusion of SPS therapy. Two additional patients received SPS three times a week chronically. Potassium was controlled in both. Reported side effects were nausea, vomiting, constipation, and hypokalemia.

Although the study numbers were small, and the mean potassium reduction moderate, this study was sufficient to convince the FDA that SPS was efficacious (2). In life-threatening hyperkalemia, serum potassium reductions need not be large to prevent cardiac arrest. It is also noteworthy that Scherr *et al.* (12) did not give SPS with a cathartic, but with water, showing

that SPS was effective in reducing serum potassium without concomitant sorbitol. Sorbitol use was first described by Flinn *et al.* in a five-patient case series, where it was used to prevent obstipation and prolonged retention of SPS (13).

Cathartic use is well known to be associated with increased stool potassium excretion and hypokalemia (14). In a stool balance study in nine healthy normokalemic subjects, 30 g of SPS given with cathartics effectively bound and removed potassium in the stool within 12 hours, peaking at approximately 4 to 6 hours. Much of the potassium removed was due to cathartic-induced diarrhea; however, the addition of SPS significantly increased potassium content in the insoluble portion of stool—indicating that potassium was bound to SPS and excreted (8). All of the subjects received intravenous potassium replacement to maintain normal serum potassium. A follow-up study (15), done in six normokalemic dialysis-dependent subjects, did not demonstrate a significant decline in potassium at 12 hours after 30 g of oral SPS, with or without a cathartic. However, the number of subjects was small, they were normokalemic, and the data show that potassium tended to increase in untreated controls, while remaining stable in subjects who received SPS or SPS/sorbitol. Statistical significance might have been achieved with a larger number of subjects. A retrospective cohort study (611 subjects with mild-moderate hyperkalemia who received SPS/sorbitol alone *versus* 108 similar controls who did not) demonstrated that oral SPS/sorbitol significantly decreased potassium in a dose-dependent fashion within 8 hours. The control cohort group, who received no therapy whatever for similar potassium elevations, had no decline at 8 hours (16).

Ion exchange resin function depends on the "selectivity" of the resin for one ion over the other (for SPS: potassium over sodium), the contact time of the resin with the ion-containing solution, the relative concentrations of the two ions, and the resin capacity. The capacity of SPS is 1 mEq of potassium per gram of resin. However, *in vivo*, sodium is only partially released, and resin efficiency is only about 33%—with a large range (17). On average, about 10 mEq of potassium will be bound and excreted per 30-g dose of SPS. Excretion also depends on extracellular potassium and sodium concentrations and colonic transit time of the resin. The studies of stool potassium excretion described above showed that SPS functioned at approximately 33% efficiency (8,15). Efficiency could be reduced by normokalemia in the subjects, and the large amount of sodium excreted in the stool due to the action of the cathartic.

Case reports describing the gastrointestinal side effects associated with SPS are of great concern, but it is very difficult to estimate incidence. Patients reported as having SPS/sorbitol-associated colonic necrosis were more likely to be uremic, after kidney transplant, or with functional or structural intestinal abnormalities. Other complications reported in association with SPS/sorbitol include aspiration pneumonitis, upper gastrointestinal injury, and rectal stenosis (2). In 752 hospitalized patients who received oral SPS/sorbitol, the only two cases of colonic necrosis were among patients within 1 week of surgery, with an incidence of 1.8% in the postsurgical patients, but less than 0.3% overall (18). Thirty-five cases of "serious bowel inju-

ries" associated with oral and rectal administration of SPS/sorbitol had been reported to the FDA by 2005 (2). The majority of reported complications are associated with SPS/70% sorbitol enemas, and studies in rats suggest that colonic necrosis is caused by 70% sorbitol rather than SPS (19). Carolina Medical, the manufacturer of SPS/33% sorbitol oral suspension, has received only one adverse event report since 1982, with 5 million doses sold yearly (2). Recently, 11 cases of colonic necrosis associated with oral SPS/sorbitol were reported at a single center over a 9-year period (2,20). Some of these patients received the 33% sorbitol formulation; 2 were postoperative and 4 had ESRD. However, this study does not report the number of subjects who received the drug. If the typical community hospital dispenses approximately 2000 doses of SPS/sorbitol per year (as estimated by Sterns *et al.* (2), that would amount to 18,000 doses over a 9-year period. The estimated incidence of colonic necrosis would be less than 0.1% per dose.

SPS has an important role in the treatment of acute hyperkalemia under austere conditions after a natural or manmade disaster (21,22). It may be used for trauma-associated hyperkalemia and as prophylaxis in dialysis-dependent patients who are not able to get to a dialysis unit (21,23). We prescribed oral SPS/sorbitol for this indication during the recent mid-Atlantic blizzard. It has been used in military medical facilities in Iraq, in the aftermath of Hurricane Katrina, and after the Haitian earthquake (24). In situations where dialysis availability is limited, SPS may be the only option for potassium removal in hyperkalemic patients, especially chronic dialysis patients.

In our experience, oral SPS/sorbitol is a useful and effective medication, and existing studies in subjects with hyperkalemia support its efficacy (12,16). We can find no studies that demonstrate that it is *ineffective* in lowering potassium in patients with hyperkalemia after 8 to 24 hours of treatment. If efficacy is in question, we do not see the impediment to a well-designed clinical trial. Clinicians should certainly follow the recommendations of the FDA regarding both Kayexalate powder and SPS/33% sorbitol. SPS/sorbitol should not be used in the immediate postsurgical period, or in patients with compromised gastrointestinal function. SPS/sorbitol enemas should not be used. They do not appear to be as effective as oral SPS, and situations in which enemas are required are associated with increased risk of colonic necrosis. We should attempt to better estimate the incidence SPS/sorbitol-associated intestinal necrosis and define the associated clinical features of patients in which it occurs. These patients may be at risk for intestinal necrosis from other causes, and demonstrating SPS crystals in conjunction with the necrotic lesion does not prove causality. The majority of patients with hyperkalemia requiring treatment with SPS likely have advanced renal failure, so it is not clear that renal failure is a risk factor for SPS/sorbitol-associated colonic necrosis beyond the fact that such patients are more likely to receive the drug. Scherr *et al.* showed that SPS is effective when given with water (12), and clinicians should consider administering it in water, especially in enema form.

Decisions regarding the continued use of SPS resins should take into account the historical context in which they were developed, the efficacy data that is available, the reasons for the

addition of cathartic agents, and a calm assessment of the patient profile most likely to be associated with serious side effects, especially colonic necrosis. Death from hyperkalemia is an unacceptable outcome. We have no data estimating the number of adverse events (hyperkalemic arrest, hospitalization, and need for acute dialysis) averted by SPS resin use, and thus it is not possible to decide whether the risks of colonic necrosis outweigh the benefits. Until there is better evidence of excess harm, or a better agent available for increasing potassium excretion, we should continue to use SPS when it is indicated. It is unwise to create a climate in which a physician attempting to control hyperkalemia can be accused of malpractice if SPS is used and if it is not.

Disclosures
None.

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