

Ion-Exchange Resins for the Treatment of Hyperkalemia: Are They Safe and Effective?

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ABSTRACT

Sodium polystyrene sulfonate (SPS), an ion-exchange resin designed to bind potassium in the colon, was approved in 1958 as a treatment for hyperkalemia by the US Food and Drug Administration, 4 years before drug manufacturers were required to prove the effectiveness and safety of their drugs. In September 2009, citing reports of colonic necrosis, the Food and Drug Administration issued a warning advising against concomitant administration of sorbitol, an osmotic cathartic used to prevent SPS-induced fecal impaction and to speed delivery of resin to the colon, with the powdered resin; however, a premixed suspension of SPS in sorbitol, the only preparation stocked by many hospital pharmacies, is prescribed routinely for treatment of hyperkalemia. We can find no convincing evidence that SPS increases fecal potassium losses in experimental animals or humans and no evidence that adding sorbitol to the resin increases its effectiveness as a treatment for hyperkalemia. There is growing concern, however, that suspensions of SPS in sorbitol can be harmful. It would be wise to exhaust other alternatives for managing hyperkalemia before turning to these largely unproven and potentially harmful therapies.

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Kayexalate (sodium polystyrene sulfonate [SPS]), an ion-exchange resin designed to exchange sodium for potassium in the colon, is approved for use in the treatment of hyperkalemia. In September 2009, the US Food and Drug Administration (FDA) posted safety labeling changes for Kayexalate powder on its web site. The warning reads, “Cases of colonic necrosis and other serious gastrointestinal adverse events (bleeding, ischemic colitis, perforation) have been reported in association with Kayexalate use. The majority of these cases reported the concomitant use of sorbitol. . . . Concomitant administration of sorbitol is not recommended.”¹

Despite this, prepackaged suspensions of SPS in sorbitol, an osmotic laxative, are still on the market and used

widely. A 6-month single-center survey from an emergency department reported 1001 patients who received SPS in sorbitol for hyperkalemia and only 188 patients who received other potassium-lowering therapies.² An unpublished hospital-wide survey of inpatient practice patterns at our own hospital yielded similar results with 1800 doses of SPS in sorbitol given in the past year, a 30% increase from a survey 2 years earlier.

Does SPS in sorbitol deserve its current popularity? Do benefits from the drug outweigh its risks? The FDA first approved Kayexalate for the treatment of hyperkalemia on June 5, 1958, 4 years before passage of the Kefauver-Harris Drug Amendments, which require drug manufacturers to prove the effectiveness of their products before marketing them. If

the FDA were to consider SPS in sorbitol and Kayexalate powder as new therapeutic agents today, would they be approved as safe and effective?

Synthetic cation-exchange resins, which became available to industry in 1935, are insoluble polymers with a molecular structure resembling a crystal lattice to which reactive carboxylic or sulfonic groups are attached. When a resin is placed in a solvent, the resin's reactive groups, which may be preloaded to form sodium, potassium, calcium, ammonium salts, or combinations of these ions, exchange their bound cations with cations dissolved in the solvent.³

Medical applications of synthetic resins were first explored in 1946.³ At approximately the same time, clinical measurements of serum potassium became available and the clinical consequences of “potassium intoxication” were first recognized.⁴ In an era when hemodialysis was not easily available, the newly accessible resins were embraced as a possible treatment for hyperkalemia.

Studies of dogs showed that a carboxylic acid exchange resin in the hydrogen cycle causes metabolic acidosis with a large increase in fecal sodium and potassium and a reciprocal decrease in urinary

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cation excretion⁵; however, even at a dosage of 30 to 60 g/d (equivalent to 200 to 400 g/d in humans), a sodium-cycled resin, which exchanges sodium rather than hydrogen for potassium, caused no change in acid-base balance, little increase in fecal potassium losses, and no change in urinary potassium excretion or plasma potassium concentration.⁵

In 1953, Evans *et al.*⁶ introduced a sulfonate resin charged with sodium, a precursor of the modern resin we know as Kayexalate. The investigators noted theoretical advantages of this preparation, because it avoids absorption of ammonium, which is metabolized to urea and causes acidosis; however, we were unable to find data then or now showing that Kayexalate or its precursors increase fecal potassium losses in experimental animals. Evans *et al.* reported uncontrolled data showing potassium binding in the stool and a hypokalemic effect in four patients with renal failure and a single normal volunteer.⁶ On the basis of necropsy studies of one patient who died of renal failure after several days of resin therapy and another patient who died of hyperkalemia 18 hours after the oral administration of the resin, the authors concluded that most potassium binding occurs in the colon. This explains why the hypokalemic effect of the resin is delayed after the first dose, reflecting the time required for resin to reach the colon, and prolonged after the last, reflecting continued delivery of orally ingested resin to the colon.

In 1961, Scherr *et al.*⁷ reported the largest clinical experience with Kayexalate suspended in water in an uncontrolled study of patients with acute and chronic renal failure, using the newly approved medication provided by the manufacturer, Winthrop Laboratories. In 23 of 30 cases, the plasma potassium fell by at least 0.4 mEq/L in the first 24 hours. Two patients with pretreatment hyperkalemia (6.1 and 7.4 mEq/L) developed hypokalemia (3.3 and 2.3 mEq/L) while receiving 40 g/d oral resin for 2 and 6 days. On the strength of this study and several smaller case series, the FDA's Drug Efficacy Study Implementation Program, charged with reviewing pre-1962

drugs that were already on the market, ruled Kayexalate powder "effective."

Even without placebo controls, development of hypokalemia in a patient with oliguria and hyperkalemia makes it difficult to deny that the resin is effective when taken for several days. Evidence of effectiveness in the crucial first 24 hours of therapy is more tenuous. Hypokalemic effects of the resin cannot be distinguished from the effects of the extremely-low-potassium diets and the concurrent administration of large quantities of dextrose used in these studies.

Soon after the introduction of Kayexalate, it was recognized that the agent could cause severe constipation and life-threatening intestinal impactions. These observations and the desire to speed delivery of the drug to the colon led to another study in 1961 of administration of resin in sorbitol, a widely used over-the-counter osmotic laxative; seven patients with oliguria were treated with three daily doses of the resin in sorbitol, and three were given sorbitol alone.⁸ A gradual steady decrease in the serum potassium over 5 days was seen in all cases. On the basis of limited data without statistical analysis, the authors concluded that "sorbitol alone is as effective as a combination."

For two decades, FDA-approved labeling for Kayexalate powder included recommendations encouraging its administration with sorbitol. In 1982, a convenient premade suspension of SPS in sorbitol was approved for commercial distribution in the United States. A survey of Drugstore and Hospital Pharmaceutical purchase data in the United States between 1985 and 1989 showed a 52% increase in the overall use of SPS during this period, all of it accounted for by growth in the use of the prepackaged suspension.⁹ By 1989, 62% of SPS was purchased as the prepackaged suspension. Today, in many hospital pharmacies, SPS in sorbitol is the only stocked preparation.

There is no evidence that adding sorbitol to potassium-binding resin makes it more effective in correcting hyperkalemia. Recent studies of patients with normokalemia and mild hyperkalemia and with ESRD found the serum potassium

concentration rose slightly (0.4 mEq/L) on placebo and did not change during the course of 12 hours in response to a single dose of 30 g of resin in water, 30 g of resin in 60 g of sorbitol, or 60 g of sorbitol alone.¹⁰

At the same time, evidence has grown that mixtures of resin in sorbitol may be harmful.¹¹ By 2005, the FDA had received 35 adverse event reports of serious bowel injuries associated with both oral and rectal administration of the mixture, many of them fatal. Extensive transmural infarction of the colon and ileum was observed with SPS crystals adherent to the mucosa and in luminal debris.^{11–13} The authors of one of the published reports identified sorbitol as the culprit, because similar bowel lesions are induced in rats with and without uremia by administering enemas of 70% sorbitol, with or without SPS, but not by giving SPS alone.¹¹ A variety of other serious complications from SPS in sorbitol have been reported, including mucosal lesions in the esophagus, stomach, and duodenum; fatal chemical pneumonitis after aspiration; and rectal stenosis as a result of a foreign body reaction to SPS crystals.^{14–16}

Responding to concerns about adverse events, recommendations for concomitant or postdosing use of sorbitol were removed from FDA-approved labeling for the powdered resin in 2005. According to a verbal communication (January 4, 2010) with the company's President and its Medical Consultant, Carolina Medical, the largest manufacturer of premixed suspensions, met with the FDA in 2006 and was allowed to continue marketing its product on the basis of the following evidence: The Carolina formulation contains 33% sorbitol and all reports of adverse gastrointestinal events followed administration of resin in 70% sorbitol; at the time, the company had received no adverse gastrointestinal event reports since the formulations's approval in 1982 (and since then only one adverse event in a critically ill patient), despite extensive use of the product (approximately 5 million doses yearly); and a study of rats conducted by the company showed that enemas of 70% sorbitol caused bowel necrosis whereas

the 33% did not. The FDA asked all other manufacturers of premixed resin to reformulate their products, and this recommendation has been in force since September 2007 (CDER DRUG INFO, DRUGINFO@fda.hhs.gov, written communication, December 3, 2009). Curiously, 70% sorbitol continues to be marketed as an over-the-counter osmotic laxative.

More recent data call the safety of the 33% sorbitol formulation into question. A study published in 2009 described 11 new cases of colonic necrosis associated with SPS in sorbitol, four of them fatal, identified over 9 years in a single center.¹³ In contrast to previous reports, only two of these cases were postoperative and only four of the patients had ESRD. Of the fatal cases, three patients were admitted with noncritical illnesses and developed symptoms of intestinal injury between 3 hours and 11 days after receiving oral SPS in sorbitol for serum potassium concentrations ranging from 5.7 to 6.8 mEq/L.¹³ Personal communications from the author of this report (C. McGowan, December 10, 2009) and from the author of another case report of a fatality¹⁷ (A. Thomas, December 17, 2009), indicate that at least some of these patients had been treated with the 33% formulation.

If Kayexalate or SPS in sorbitol were presented to the FDA as new drugs with the data available today, it is doubtful that either would pass muster. Clinicians must weigh uncontrolled studies showing bene-

fit against uncontrolled studies showing harm. It would be wise to exhaust other alternatives for managing hyperkalemia before turning to these largely unproven and potentially harmful therapies.

DISCLOSURES

None.

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