To practicing nephrologists, few drugs are more familiar than sodium polystyrene sulfonate (SPS) (Kayexalate). Generally given in a premixed preparation with sorbitol, Kayexalate is widely used for the treatment of elevated potassium levels, with millions of doses prescribed every year. Despite recent safety concerns—including reports of colonic necrosis, leading to a safety warning from the U.S. Food and Drug Administration—SPS plus sorbitol continues to be available and prescribed.

Prompted by this new attention to an old drug, Richard Sterns, MD, of Rochester General Hospital, University of Rochester School of Medicine and Dentistry, NY, reviewed 50 years of published data on the use of SPS for hyperkalemia and reached some surprising conclusions. “We found no rigorous scientific evidence showing that ion exchange resins are effective in ridding the body of excess potassium,” said Sterns. “We also found some evidence showing that, on rare occasions, they can be harmful. “We suspect that if ion exchange resins were introduced today, they would not be approved.” The invited commentary by Sterns—with co-authors Maria Rojas, MD, Paul Bernstein, MD, and Sreedevi Chennupati, MD—appears in the May Journal of the American Society of Nephrology.

Grandfathered drug predates modern drug approval process

Sodium polystyrene sulfonate is an ion exchange resin designed to exchange sodium for potassium in the colon. It may be given orally or by enema. Because of its potential

New Questions on Old Drug for Hyperkalemia

Nephrologists Have Used Kayexalate for Decades—But Does It Really Work?

By Timothy O’Brien

This DPP-4 inhibitor, which stimulates the pancreas to make more insulin after eating a meal, was one of the 26 new compounds approved by FDA in 2009. Saxagliptin is marketed by AstraZeneca and Bristol-Myers Squibb. The companies also have another potential type 2 diabetes drug in development (see below).

Liraglutide (Victoza®) for type 2 diabetes

Liraglutide (Victoza®) was approved by the FDA on Jan. 25 for the treatment of type 2 diabetes in adults, but...
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tial to cause severe constipation, SPS is usually given with sorbitol, a widely used and well-tolerated osmotic laxative.

The Kayexalate name is still widely used, even though generic preparations are most commonly given. "Kayelate has come synonymous with SPS—it's kind of like Klenex or Xerox," said Sterns. "When Kayexalate is written, what's given is a premixed preparation of the SPS resin in sorbitol.

Because it has FDA approval, one would assume that there's adequate evidence supporting its effectiveness. However, Kayexalate was approved in 1958—four years before passage of the Kefauver-Harris Drug Amendments. Under the 1938 Federal Food, Drug, and Cosmetic (FD&C) Act, drug manufacturers were required to demonstrate only that their products were safe. After the Kefauver-Harris Amendments, manufacturers had to provide scientific evidence that their products were effective as well as safe.

But drugs like Kayexalate, which had already been approved under the FD&C Act, were "grandfathered" and allowed to remain on the market—despite some early concerns. The evidence that Kayexalate was effective, but it was based on what today would be considered anecdotal evidence," said Sterns. The evidence included a 1961 paper by Scherr et al. (N Engl J Med 1961; 264:115–119), which reported that 23 of 30 patients had at least a 0.4 mEq/L drop in plasma potassium during the first 24 hours on Kayexalate. To this day, the paper by Scherr et al. remains the largest published experience with Kayexalate. Based on the Scherr report and a few others—including observations of patients who actually became hypokalemic while receiving Kayexalate—the FDA concluded that the drug was effective.

What about sorbitol?

The efficacy evidence on sorbitol is even sketchier—another 1961 paper concluded that "sorbitol alone is as effective as a standard operating procedure years ago, which suggested that this was more common than had been previoulsy thought."

The paper by C.E. McGowan, et al. (South Med J 2009; 102:493–497), reported 11 confirmed cases of intestinal necrosis temporally associated with administration of SPS. "This report also showed the colonic necrosis could occur in people who were not that ill," said Sterns. "Some were patients who had just been admitted for some reason and found to be hypokalemic—often mild hypokalemic—and then subsequently developed colonic necrosis."

The reports have prompted a re-evaluation of the risks versus benefits of Kayexalate. "We're at the point now where people have really begun to question if this drug is potentially dangerous," said Emmet. "If it doesn't do much, then why are we using it?"

In September 2009, the FDA issued a warning against concomitant administration of Kayexalate with sorbitol—although the combination product remains on the market. Sterns spoke to the manufacturers of the most widely used generic preparation of SPS plus sorbitol. "They actually make some good points," said Sterns. "They have received very few reports, actually just one report of colonic necrosis, which could be a smaller concentration of sorbitol than most of the cases in the literature that have described harm."

This report contains 33 percent sorbitol, whereas the reports of adverse events have come in patients receiving 70 percent sorbitol. Sterns added, however, that at least some of the patients in the Southern Medical Journal report had received lower concentrations of sorbitol.
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“We need to be more rigorous in looking for this complication.”

Amid safety concerns, efficacy still unknown

Meanwhile, there are still no convincing data to answer the most pressing question: Does Kayexalate lower high potassium levels? When they started their review, Sterns and colleagues knew that Kayexalate was a grandfathered product that hadn’t been subjected to the rigorous efficacy evaluations required for today’s new drugs. “But what I had not realized was that there’s no evidence this preparation increases fecal potassium losses—even in animals,” said Sterns. “And in humans, there are no controlled data.”

Emmett’s group has performed research showing no change in serum potassium levels in end stage renal disease patients with normokalemia or mild hyperkalemia receiving SPS alone or SPS plus sorbitol. “This really casts doubt that Kayexalate was doing very much at all,” according to Sterns.

Another review (Nephrol Dial Transplant 2003; 2215–2218) has questioned the theoretical basis of Kayexalate’s potassium-lowering effect. “Based on in vitro binding characteristics of Kayexalate, the only favorable location for this exchange of Na+ for K+ in the gastrointestinal tract is in the colon,” according to Kamel Kamel, MD, of the University of Toronto. However, the amount of K+ that is delivered to the colon is small—about 5 mmol/day.

“In humans, active secretion of potassium in the gastrointestinal tract occurs in the recto-sigmoid portion of the colon,” said Kamel. “One possible theoretical benefit to the use of cation-exchange resins is that, if they were to lower the potassium concentration in luminal fecal water, the net secretion of potassium by the colon would be enhanced.” However, Kamel pointed out that several other cations are available in the colon to exchange for resin-bound sodium.

“Even if patients with ESRD had an adaptive increase in colonic potassium secretion, and if resins were effective in lowering the potassium concentration in fecal water and hence stimulate this process, stool volume would be limiting,” Kamel added. “There are data to show that the addition of resins does not significantly enhance the excretion of potassium beyond the effect of diarrhea induced by osmotic or secretory cathartics.”

Research needed—but other options available

Despite the lack of data, Kayexalate continues to be prescribed and administered. “We’ve looked at our local practice patterns, and I don’t think they’re unique,” said Sterns. “The administration of Kayexalate has become a pretty monosynaptic reflex to the finding of hyperkalemia—even in patients who have only mild renal impairment and would be better managed with just diuretic and by stopping potassium-sparing agents.”

Emmett agrees that giving Kayexalate is still a reflex for many physicians. “You see a potassium level that’s very high, and you generally throw the whole kitchen sink at the patient … three or four different things, one of which is Kayexalate. And then the potassium comes down, and nobody knows exactly which of these various therapies was most important in achieving that result.”

“The risk to a single patient is unlikely to be very high,” according to Sterns. “But because of the large number of Kayexalate doses given every year, I think we’re exposing an awful lot of people to potential risk.” Sterns and colleagues recommend that physicians “exhaust other alternatives” for treatment of hyperkalemia before turning to ion exchange resins.

Emmett noted that there are other good options for the acute treatment of hyperkalemia, including intravenous insulin and glucose, inhaled beta-2 agonists, and even sodium bicarbonate—“which may or may not be very effective but is probably safe,” according to Emmett. “Diuretics are also useful, if the patient has reasonable kidney function. If kidney function is very poor, then dialysis is the most effective way to reduce the potassium concentration urgently.”

A randomized trial would be needed to demonstrate the safety and efficacy of Kayexalate, and SPS plus sorbitol, in the treatment of hyperkalemia—although it is unclear who would perform such a study. “A good start might be a study in experimental animals, which has never been done,” said Sterns. “And of course, a controlled trial to show increased fecal excretion.”

Given the other effective options, Emmett questions whether the issue of Kayexalate effectiveness is really all that pressing. Of the various options for acutely lowering potassium, “Kayexalate is clearly the least powerful,” he said. “I don’t think patients would be harmed or physicians would be very upset if a recommendation came out that it should not be a component of the treatment regimen to acutely reduce plasma potassium levels.”

Kayexalate Timeline

- Late 1940s to early 1950s: Initial studies of medical applications of synthetic cation-exchange resins.
- 1961: Study by Scherr et al in 30 patients—still the largest published experience with Kayexalate. Recommendations to give Kayexalate with sorbitol because of potential for severe constipation.
- 1962: Kefauver-Harris Amendments passed; Kayexalate receives “grandfathered” drug designation.
- 1982: Premade preparation of Kayexalate plus sorbitol approved for commercial distribution—still the most widely used preparation.
- 2005: Reports of serious bowel injuries associated with Kayexalate plus sorbitol. FDA recommendation for administration with sorbitol removed.
- 2009: FDA issues warning against giving Kayexalate with sorbitol. Premixed product (containing 33% sorbitol) remains on market.