Letter to the Editor

Taking a Second Look at Kayexalate

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To the Editor:

Sodium polystyrene sulfonate (SPS) [*Kayexalate*], an ion exchange resin, has been used to treat hyperkalemia for more than 50 years. During this time, evidence-based medicine has made exponential progress. As much as possible, we use methods and medications that are proven to be effective in randomized controlled trials. A review of studies supporting the use of SPS to treat hyperkalemia leaves me wondering why SPS is still used. By today's standards, the studies supporting the use of SPS for hyperkalemia would be identified as poorly designed case studies, without randomization, without statistical analysis, and without a large sample size. Admittedly, it is somewhat unfair to judge 50-year-old studies by today's standards. But isn't it questionable to treat a patient with a medication just because that's the way we've always done it? Especially if it is ineffective and possibly dangerous?

GUIDELINES

The 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care include advanced adult cardiovascular life support (ACLS) in Part 8. A suggested course of treatment for hyperkalemia is provided in Part 12: Cardiac Arrest in Special Situations: Part 12.6 Cardiac Arrest Associated With Life-Threatening Electrolyte Disturbances.¹ The treatment includes calcium, albuterol, sodium bicarbonate, insulin, dextrose, and *Kayexalate*. This course of treatment is based on weak evidence. In Part 2 of the guideline, the AHA describes the evidence as "Class IIb, Level of Evidence C," which it defines as, "Recommendation's usefulness/efficacy less well established...Only diverging expert opinion, case studies, or standard of care."^{2(p5660)} In the AHA guidelines, this is the weakest level of evidence that can be recommended. Any further downgrade of this recommendation would put it into the risk is greater than benefit category. It is my opinion that just such a downgrade is appropriate.

To further support my observation, I enlist a published author. In a 2009 clinical review, Nyirenda et al wrote, "Guidelines for treatment of hyperkalaemia are based on consensus or expert opinion because of a lack of controlled clinical trials."³

HISTORY

The Food, Drug, and Cosmetic Act (FDCA) was passed in 1938.⁴ The FDCA is the basis for modern pharmacy law. "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 [and safety] of their products before marketing them."^{5(p733)} In a review, Mahoney et al did a literature search back to 1966 that identified 1,974 potentially relevant articles. They concluded, "There is no randomised [sic] evidence that potassium-exchange resins are effective."^{6(p14)}

Four of the early studies that supported the use of ion exchange resins for treatment of hyperkalemia were published by Bernard et al,⁷ Palmer et al,⁸ Scherr et al,⁹ and Flinn et al.¹⁰

The study by Scherr et al, published in the *New England Journal of Medicine* (1961), used SPS. This was the largest of the aforementioned studies, including 32 cases. In 2 of these cases, SPS was administered over a period of months. If *Kayexalate* was effective at reducing potassium, why did this treatment not result in dangerously low levels of potassium? For the other 30 cases, the duration of therapy was 1 to 6 days. A statement from the article reads, "As shown in Table 1, 30 patients either demonstrated a significant fall in plasma potassium or failed to show any increase in these values during the period observed."^{9(p118)} Since no statistical analysis was done, the results are only significant because the authors declare them so. Further, they included "failed to show any increase" as an outcome indicating efficacy of treatment.

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Two of the other studies showed serum potassium decline coincidental to increased urine output.^{7,8} One showed a greater decline in serum potassium when sorbitol only was administered than with sorbitol and SPS.¹⁰

More current and better designed studies have been unable to demonstrate efficacy of SPS for treating hyperkalemia.^{11,12} Published clinical commentaries have declared that the potassium-lowering effect of SPS is indistinguishable from laxatives or extremely low-potassium diets.^{5,13}

None of the early studies provide strong evidence for the efficacy of SPS. The studies are small, uncontrolled, and poorly designed. There are too many variables. More recently, authors have highlighted some of these limitations of the early studies, as they were unable to validate the results in studies of their own.^{11,12} Furthermore, the literature is scattered with recent commentaries that question the safety of *Kayexalate*.¹⁴⁻¹⁶

ALTERNATIVES

The 2 best alternatives to SPS resin for the elimination of potassium are dialysis or, if the patient has preserved kidney function, loop diuretics and increased fluid intake, oral or intravenous (which may not be appropriate in a heart failure patient). These alternatives are well known and widely published; these options are also included in the AHA guidelines.^{1,2,5,12}

CONCLUSION

Critical analysis of the original studies explains why the AHA cannot make a stronger recommendation for SPS and challenges the use of SPS to treat hyperkalemia.

REFERENCES

- Vanden Hoek TL, Morrison LJ, Shuster M, et al. Part 12: Cardiac arrest in special situations: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122:S829-S861
- Sayre MR, O'Connor RE, Atkins DL, et al. Part 2: Evidence evaluation and management of potential or perceived conflicts of interest: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122:S657-S664.
- Nyirenda MJ, Tang JI, Padfield PL, et al. Hyperkalaemia. *Br Med J*. 2009;339:1019-1024.
- Aboud R. *Pharmacy Practice and the Law*. 5th ed. Boston: Jones and Bartlett; 2008.
- Sterns RH, Rojas M, Bernstein P, et al. Ion-exchange resins for the treatment of hyperkalemia: Are they safe and effective? *J Am Soc Nephrol*. 2010;21:733-735.
- Mahoney BA, Smith WAD, Lo D, et al. Emergency interventions for hyperkalaemia (review). *Cochrane Database Syst Rev*. 2009;3.
- Bernard H. Cation exchange resins in the treatment of hyperkalemia. *Am Med Assoc Arch Surg*. 1958;77:703-708.
- Palmer RA. The treatment of hyperkalaemia by carboxylic acid resins in the upper and lower gastrointestinal tract. *CMAJ*. 1959;80:432-435.
- Scherr L, Ogden DA, Mead AW, et al. Management of hyperkalemia with a cation-exchange resin. *N Engl J Med*. 1961;264:115-119.
- Flinn RB, Merrill JP, Welzan WR. Treatment of the oliguric patient with a new sodium ion exchange resin and sorbitol: A preliminary report. *N Engl J Med*. 1961;264:111-115.
- Emmett M. Effect of three laxatives and a cation exchange resin on fecal sodium and potassium excretion. *Gastroenterology*. 1995;108.3:752-760.
- Gruy-Kapral C, Emmett M, Santa Ana CA, et al. Effect of single dose resin-cathartic therapy on serum potassium concentration in patients with end-stage renal disease. *J Am Soc Nephrol*. 1998;1924-1930.
- Sood MM, Sood AR, Richardson R. Emergency management and commonly encountered outpatient scenarios in patients with hyperkalemia. *Mayo Clin Proc*. 2007;82:1553-1561.
- Rogers BR, Li SC. Acute colonic necrosis associated with sodium polystyrene sulfonate (*Kayexalate*) enemas in a critically ill patient: Case report and review of the literature. *J Trauma*. 2001;51:395-397.
- Harel Z, Harel S, Shah PS, Wald R, Perl J, Bell CM. Gastrointestinal adverse events with sodium polystyrene sulfonate (*Kayexalate*) use: A systematic review. *Am J Med*. 2013;126(3):264.e9-264.e24.
- Bombardier A, Woosley JT, Kshirsagar AV. Colonic necrosis due to sodium polystyrene sulfate (*Kayexalate*). *Am J Emerg Med*. 2009;27:753.e1-753.e2. ■