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Editorial comment

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The chronic kalaemia conundrum

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In this issue, Ritz and Pitt discuss mineralocorticoid-receptor blockade in patients with chronic kidney disease (CKD), the propensity to develop hyperkalaemia, and present a novel suggestion of what to do about it. Actually, the risk of hyperkalaemia in CKD patients may be less of a lethal problem than hypokalaemia; however, hyperkalaemia seems to pack the imagination of clinicians more than hypokalaemia [1]. Nonetheless, hyperkalaemic CKD patients indeed have a risk of death, and the ingestion of antihypertensive drugs blocking the renin–angiotensin–aldosterone system certainly appears to contribute [2]. Ritz and Pitt introduce us to a novel polymeric potassium binder, RLY5016, which packs its potassium-binding punch in the form of 100-µm beads. Clinical experience with RLY5016 is reported in a study assessing RLY5016 in patients with chronic heart failure. In that study, patients receiving renin–angiotensin–aldosterone-blocking drugs were randomized to RLY5016 or placebo [3]. The study group had a lower potassium level, by −0.52 mmol/L, while fewer patients developed hyperkalaemia, 7 compared with 25% with placebo. On the downside, 6% of patients developed hypokalaemia, compared with none with placebo. RLY5016 is not administered with a laxative (no sorbitol) and has not been associated with the occurrence of bowel necrosis. Interference with therapeutic drug absorption thus far seems to involve only a 30% reduction in the bioavailability of valsartan and rosiglitazone. However, the pharmacological testing of this issue may not yet be complete. Relypsa is a clinical-stage biopharmaceutical company that is developing RLY5016.

I did my best to learn more about the basic pharmacology of RLY5016, but failed miserably. There are four PubMed citations to date (24 July 2013) and three of those are reviews with hymns-of-praise but little hard information. No structural information on RLY5016 was given. Of course, I would have liked to see some data from normal volunteers receiving a known and fixed dietary potassium intake, along with stool collections, and a comparison with sodium polystyrene sulphonate. For this cation exchange resin, which is also a polymer derived from polystyrene but containing sulfonic acid or sulphonate functional groups, the mode of action is well known. The ion exchange functions effectively as shown (Figure 1) in this case applied to water softening and not to potassium removal.

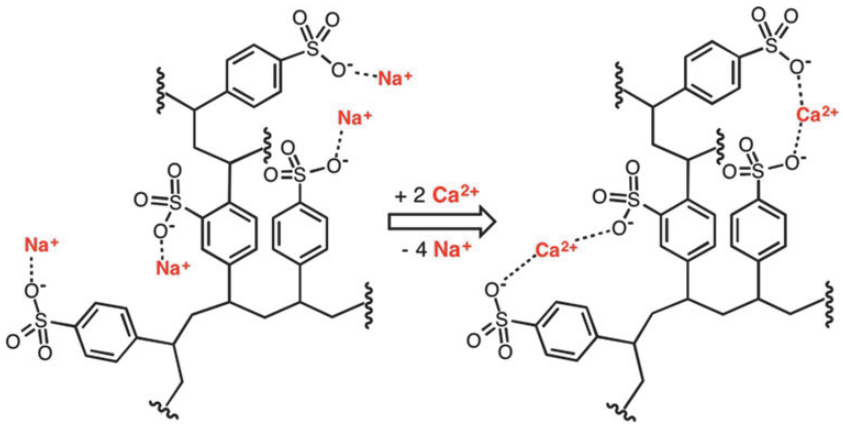

Fig. 1. An idealized image of water softening process involving replacement of calcium ions in water with sodium ions donated by a cation exchange resin is shown. The process for potassium is similar (obtained from https://en.wikipedia.org/wiki/Polystyrene_sulfonate).

Those of us predating the 'evidence-based era' generally did as we were told by our chiefs-of-service, back in the 'eminence-based era'. Way back then, dialysis was the last-resort option shortly before death, so I administered a lot of sodium polystyrene sulphonate. Anecdotally, sodium polystyrene sulphonate led to laparotomy for bowel obstruction in some patients not receiving sufficient quantities of sorbitol. Potassium removal appeared to be a function of how much sorbitol was given. Perhaps the diarrhea was more important than the sodium polystyrene sulphonate. An alternative was the sodium polystyrene sulphonate enema. This therapeutic option tortured not only the patients but also the nurses.

I suppose that sodium polystyrene sulphonate must go. A decade ago I was very much interested in an *N Engl J Med* report on a very ill patient with bowel necrosis of unknown aetiology [4]. Ten years later, everyone knows about the association between oral sodium polystyrene sulphonate given with sorbitol and colonic necrosis, so I will not dwell on the subject here [5, 6].

Are there still other options for managing patients with, or at risk of, developing hyperkalaemia? Again, PubMed was not helpful, but an Internet website was informative (http://clinicaltrials.gov/ct2/show/NCT01737697?term=hyperkalemia&rank=4). I learned that a safety and efficacy study is currently recruiting subjects to test the efficacy of zirconium silicate in patients with mild-to-moderate hyperkalaemia. Thus, RLY5016 could be faced with competition. Spironolactone was first introduced over 50 years ago [7]. We will be faced with the prospects of paying much more for a compound to protect from the side effects than we will for the compound that prolongs the lives of heart failure patients.

Conflict of interest statement. None declared.

(See related article by Ritz and Pitt. Mineralocorticoid receptor blockade—a novel approach to fight hyperkalaemia in chronic kidney disease. *Clin Kidney J* 2013; 6: 464–468)

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