Novel Oral Potassium Binders

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In this pandemic era, the curtailment of patient exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by decreasing emergency room (ER) visits, reducing hospitalizations, and diminishing blood draws is a real benefit. Also, medical treatment of hyperkalemia and lessening of the burden on acute dialysis staff and available machines will help to prepare for any surge.

Financial data should be collected, and if the results are positive, actions should be taken to make these agents easily accessible, thereby potentially helping avoid ER visits, subsequent hospitalizations, and even the need for acute dialysis. Different practices should work on specific protocols to better manage hyperkalemia and include those protocols in quality improvement projects, i.e., regular assessment of the quality metrics, followed by appropriate action plans. This paradigm shift in the management of chronic hyperkalemia should open the doors for challenging endpoint studies in patients with kidney and cardiovascular diseases, where life-saving medications, such as RAAS inhibitors, mineralocorticoid receptor antagonists, and even beta-blockers, can be potentially titrated to the maximum dose. Another area of related interest may be how a more liberal diet affects the outcomes, nutritional status, and quality of life of patients (3). Many foods with health benefits (fruits and vegetables) also tend to be high in potassium.

There is a big push for home dialysis and urgent dialysis starts. A safe, effective, and well-tolerated potassium binder can make such a transition perhaps less challenging, particularly if hyperkalemia is one of the reasons driving the need for urgent-start kidney replacement therapy. This will give time for appropriate dialysis access placement, as well as evaluation and training, which will potentially translate into improved outcomes, including retention of patients on such dialytic modalities. The same applies to preemptive kidney transplantation, where a patient gets a transplant before going on dialysis. This is usually only possible if the patient has a potential living kidney donor, as the waiting time for a deceased kidney donation is quite protracted in most cases. However, at times, the living donor evaluation process may need to be delayed. A safe and effective K+ binder may help bridge the gap to a successful transplantation when the donor is ready.

In the future, cross-specialty training in hyperkalemia management is foreseeable. This should include trainees as well as clinical practitioners. Nephrology, cardiology, and diabetes specialists and primary care physicians should work collaboratively to optimize the medical management of patients, including keeping them on the medications and appropriately adjusted dosages as per kidney function.

The ultimate hope is that these novel oral K+ binders will help facilitate enhanced organ protection and at the same time, cause less hyperkalemia.

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Table 1. Agents approved for managing hyperkalemia

	Sodium polystyrene sulfonate (Kayexelate®) *15 g qD-QID (PO)* *30-50 g qD-BID (PR)*	Patiromer (Veltassa®) *8.4 g qD (PO), titrate up to 16.8 g or 25.2 g qD*	Sodium zirconium cyclosilicate (Lokelma®) *10 g TID (PO) for initial correction of K+ (for ≤ 48 h), then 5 g qOD or 15g qD for maintenance*
Year of Approval (US FDA)	1958	2015	2018
Mechanism of Action Selectivity for K^+ binding	Na^+ K^+ exchange resin Non-selective: also binds Ca^{2+} and Mg^{2+}	Ca^{2+} K^+ exchange polymer Non-selective: also binds Na^+ and Mg^{2+}	Crystalline compound traps K^+ in exchange for Na^+ and H^- Highly selective: also binds NH^{4+}
Components	Na^+ 1.5 g per 15 mg dose ± Sorbitol 20 g per 15 g dose	Ca^{2+} 1.6 g per 8.4 g dose Sorbitol 4 g per 8.4 g dose	Na^+ 400 mg per 5 g dose
Onset of Action	Variable	7 hours	1 hour
Site of Action	Colon	Distal colon predominantly	Entire GI tract
Separation required with other oral medications	3 hours before and 3 hours after	3 hours before and 3 hours after	2 hours before and 2 hours after
Adverse events	Nausea, vomiting, diarrhea, constipation, edema, GI bleeding, **bowel necrosis/ perforation** (SAE)	Nausea, diarrhea, constipation, hypomagnesemia	Nausea, diarrhea, constipation, peripheral edema

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Does Veverimer Hold the Future for Metabolic Acidosis?

By Katherine Kwon

Veverimer is a novel agent for the treatment of metabolic acidosis in chronic kidney disease (CKD). It is a nonabsorbable polymer that selectively binds hydrochloric acid, leading to excretion of excess acid via the gastrointestinal tract. Veverimer completed a phase 3 clinical trial, demonstrating correction of serum bicarbonate when compared to placebo (1). However, in August 2020, the US Food and Drug Administration (FDA) declined to approve veverimer, requesting additional information on the likelihood of clinical benefit. This prompted manufacturer Tricida to create the VALOR-CKD trial. This ongoing trial will evaluate veverimer's efficacy against placebo on progression of kidney disease (2).

Metabolic acidosis in CKD is associated with a wide range of deleterious effects, including impaired muscle function, decreased bone density, and accelerated progression to end-stage kidney disease. The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for management of CKD recommend treating metabolic acidosis with supplemental bicarbonate (3). However, bicarbonate and citrate (which metabolizes to bicarbonate) formulations include cations, such as sodium, potassium, or calcium, all of which can pose potential challenges in kidney patients who take them in large doses.

Veverimer allows for the correction of metabolic acidosis without the risks of the exogenous cations. It remains to be seen, however, if this correction leads to clinically meaningful outcomes for kidney patients. The VALOR-CKD trial seeks to answer this question but as a placebo-controlled trial, will not test efficacy against the current therapies in use. Existing therapies (sodium bicarbonate) are supported by several trials (albeit small) but do not have specific FDA approval for treating metabolic acidosis in CKD. Without a head-to-head trial, nephrologists and patients with kidney disease will need to decide if the anticipated extra cost of veverimer is worth it.

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