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Review

New approaches to hyperkalemia in patients with indications for renin angiotensin aldosterone inhibitors: Considerations for trial design and regulatory approval

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ABSTRACT

Hyperkalemia is a common clinical problem, especially in patients with chronic kidney disease, diabetes mellitus, or heart failure. Treatment with renin angiotensin aldosterone system inhibitors exacerbates the risk of hyperkalemia in these patients. Concern about hyperkalemia can result in the failure to initiate, suboptimal dosing, or discontinuation of renin angiotensin aldosterone system inhibitor therapy in patients; effective treatments for hyperkalemia might mitigate such undertreatment. New treatments for hyperkalemia in development may offer better efficacy, tolerability and safety profiles than do existing approved treatments. These compounds might enable more eligible patients to receive renin angiotensin aldosterone system inhibitor therapy or to receive renin angiotensin aldosterone system inhibitors at target doses. The evidence needed to support a treatment claim (reduction in serum potassium) differs from that needed to support a prevention claim (preventing hyperkalemia to allow renin angiotensin aldosterone system inhibitor treatment). Thus, several issues related to clinical trial design and drug development need to be considered. This paper summarizes and expands upon a discussion at the Global Cardiovascular Clinical Trialists 2014 Forum and examines methodologic considerations for trials of new potassium binders for the prevention and management of hyperkalemia in patients with renin angiotensin aldosterone system inhibitor indications.

1. Introduction

Hyperkalemia, which results from impaired potassium handling, commonly occurs in chronic kidney disease (CKD), type-2 diabetes mellitus, and heart failure [1]. Hyperkalemia is a well-understood contributor to the risk of arrhythmia and sudden death, although the shape of the relationship is not fully known [2].

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Renin–angiotensin–aldosterone system inhibitors (RAASi) are guideline-recommended therapies that reduce morbidity, slow progression of renal disease, or prolong survival in several disease states (Table S1). These drugs increase the risk of hyperkalemia, especially in CKD patients or those treated with multiple RAASi [3,4].

Hyperkalemia rates vary from 2% to >50% in observational studies, depending on the patient population and CKD severity [5,6]. Patients with risk factors for hyperkalemia (e.g., older age, diabetes mellitus, CKD, heart failure with reduced ejection fraction [HFrEF]) [1] are also those who receive the greatest absolute benefit from RAASi [7]. Several analyses have shown that the beneficial effects of RAASi on primary outcomes in large RAASi trials are independent of the development of hyperkalemia [8–10].

Other than RAASi discontinuation or dose reduction, options are limited for the treatment or prevention of hyperkalemia. Patients often have difficulty limiting dietary potassium intake [11], and high potassium foods are otherwise desirable for patients with underlying diseases predisposing to hyperkalemia. Sodium (or calcium) polystyrene sulfonate (SPS, CPS) may be poorly tolerated and have occasionally caused colonic necrosis in sick patients [12]. Because SPS uses sodium and CPS uses calcium as the exchange counter-ion for potassium, their administration may lead to increases in serum levels of these cations. Caution is advised when SPS is administered to patients who cannot tolerate sodium (i.e., severe congestive heart failure, severe hypertension, or marked edema) or calcium (i.e., vascular calcification) loads [13]. Further, the magnitude of their effect on serum potassium is not well characterized [12,14]. Other standard treatments shift potassium into cells but do not remove potassium (e.g., insulin and dextrose, inhaled β_2 agonists, sodium bicarbonate) or are expensive and invasive (hemodialysis) [15]. Thus, an unmet need remains for therapies to treat and prevent hyperkalemia in high-risk patients, especially those for whom RAASi have the potential to reduce major morbidity or prolong survival [7].

New treatments for hyperkalemia in development may offer better efficacy, tolerability and safety profiles than approved treatments [16–21]. New compounds might enable more eligible patients to receive RAASi therapy at appropriate doses. Using potassium binders to increase RAASi uptake appears clinically reasonable, but it raises several important questions. To what extent would potassium binders permit optimization of RAASi therapy and would such an effect translate into improved clinical outcomes? Will their efficacy, safety, and tolerability profiles justify continuous or frequent intermittent use? These issues were discussed during the 11th Global Cardiovascular Clinical Trialists Forum held in Washington, D.C., in December 2014 among renal and cardiovascular clinical trialists, clinicians, biostatisticians, National Institutes of Health (NIH) scientists, European and U.S. regulators, and pharmaceutical industry scientists. At the time of the meeting, two potassium binders, patiromer and sodium zirconium cyclosilicate (ZS-9), were in late stages of clinical development and served as a backdrop for discussions (Table S2). This paper examines methodologic considerations for designing trials of new potassium binders for the prevention and management of hyperkalemia with the aim of optimizing RAASi therapy.

2. New drugs in development for hyperkalemia

2.1. Patiromer

Patiromer is a free-flowing powder of small (on average ~ 100 μm), low-swelling, spherical beads which is administered as an oral suspension in a small amount of water. Patiromer is an insoluble cation exchange polymer that binds potassium in the gastrointestinal lumen, predominantly in the distal colon, resulting in increased fecal potassium excretion [17,18,22]. A study of radiolabeled patiromer in dogs demonstrated that it is not absorbed [23]. The polymer is tightly cross-linked for minimal swelling. Calcium was chosen as the exchange counter-ion instead of sodium to avoid the potential for sodium and fluid retention [22].

2.2. Sodium zirconium cyclosilicate

Sodium zirconium cyclosilicate (ZS-9) is a non-absorbed, insoluble powder designed to bind potassium ions selectively over certain other cations (e.g., calcium or magnesium) and exchange them for sodium and hydrogen [16,24]. Partial (50%) protonation (Na-H) was chosen rather than 100% sodium because of concerns related to sodium loading, and calcium was not chosen because of concerns about calcium loading and possible vascular calcifications in patients with CKD [24]. ZS-9 is an inorganic cation exchange crystalline compound, containing <8% sodium (total weight) [24]. ZS-9 is a free-flowing powder that does not absorb water or swell in the gastrointestinal tract.

3. Unmet medical needs in hyperkalemia management: strategies to maintain RAAS inhibition

Concerns about inducing worsening renal function or hyperkalemia may lead clinicians to avoid RAASi initiation or dose titration in high-risk patients [25]. For example, cautious use or avoidance of mineralocorticoid receptor antagonists (MRAs) is recommended in HFrEF patients with estimated glomerular filtration rates (eGFR) <30 mL/min/1.73 m^2 or serum potassium >5 mEq/L [26,27].

The percentage of CKD or diabetes patients not treated with RAASi because of actual or perceived hyperkalemia risk is not well known. The United States Renal Data System reported that RAASi use across CKD stages was 43%–47% within 2 years prior to the initiation of therapy for end-stage disease; this proportion fell to 33%–37% within the first quarter after end-stage disease therapy initiation [28]. A working hypothesis is that new potassium binders might be used preventively to enable RAASi use in patients with a history of hyperkalemia due to RAASi or who are suspected to be at high-risk for developing hyperkalemia after RAASi initiation.

The literature suggests that MRAs are not prescribed in 18%–40% [25,29,30] of eligible HFrEF patients, because the eGFR or serum potassium thresholds were met, or because of a perceived hyperkalemia risk. The European Society of Cardiology heart failure long-term registry reported that hyperkalemia was a reason for not prescribing ACE-inhibitors or ARBs in 6.5% and MRAs in 35.4% of the 7401 registry participants with ambulatory chronic HFrEF [25].

A hyperkalemia prevention study was conducted evaluating patiromer versus placebo in a 4-week, double-blind pilot trial of normokalemic patients with HFrEF who were starting spironolactone therapy [18]. After 4 weeks, more patients in the patiromer group reached spironolactone 50 mg/day, and the incidence of hyperkalemia was lower than in the placebo group [18]. Testing this prevention strategy in larger, longer-term, randomized, controlled trials is warranted.

Intermittent potassium binder use might also be feasible and deserves further study. Intermittent use might be applicable in RAASi-treated patients with borderline hyperkalemia who need treatment when serum potassium or serum creatinine (obtained at routine intervals) rises above a certain threshold, but who do not require chronic treatment. Safety concerns unique to intermittent use would need to be studied, including the appropriate intervals for monitoring serum potassium and renal function, as well as the time to achieve clinically significant reductions in serum potassium [31,32].

New potassium binders might also enable study of patients that have been excluded or underrepresented in RAASi clinical trials, e.g. those with eGFR <30 mL/min/1.73 m^2 or serum potassium >5.0–5.5 mEq/L (Table 1). Whether their response to RAASi, from a perspective of either efficacy or safety, might differ in a meaningful way is a matter of debate and perhaps warrants further investigation. Studies in these populations might become feasible if potassium binders are used to mitigate the hyperkalemia risk.