Nephrology and Renal Diseases

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Editorial

Hyperkalemia

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Hyperkalemia is a well-known and vexing problem that is commonly seen in the treatment of patients with heart failure and kidney disease [1]. Angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARBs) and aldosterone antagonists are collectively referred to as renin–angiotensin–aldosterone system (RAAS) inhibitors and have well known beneficial value in managing patients with heart failure and kidney disease; however, hyperkalemia can be a major barrier in introducing or up-titrating these medications. Strict diets and diuretics are not always successful in preventing hyperkalemia associated with these medications. Thus, nephrologists and cardiologists find themselves oscillating between adding and removing RAAS inhibitors.

Hyperkalemia is usually defined as a serum potassium greater than 5.0 mEq/l. Severe hyperkalemia can be lethal and is usually defined as a serum level greater than 6 mEq/l. Disturbance of the ratio of intracellular to extracellular potassium leads to cardiac cell membrane instability with subsequent life-threatening arrhythmias. The incidence and prevalence of hyperkalemia in the general population are largely unknown, but in hospitalized patients, studies have reported an incidence of 1-10 percent [2].

Reductions in both cardiovascular morbidity and mortality with RAAS inhibitors have been well demonstrated in several studies including SOLVD (enalapril in heart failure), EUROPA (perindopril in stable coronary disease) and HOPE (ramipril in patients with high cardiovascular disease risk). Hence, the cornerstone of delaying progression of both renal and cardiac disease in general practice has been neuro hormonal blockade of the RAAS at different levels with close monitoring for the challenging side effect of hyperkalemia. It is well established that impaired potassium homeostasis, attributable to hyporeninemic hypo aldosteronism, can occur with aging, diabetes and progressive loss of functioning nephrons [3-5]. Moreover, hyperkalemia has been associated with increases in all-cause mortality and hospitalization [2]. Advanced kidney disease, diabetes mellitus, coronary artery disease, and peripheral vascular disease are all independent risk factors for hyperkalemia [6]. Consequently, these patients are more vulnerable to the detrimental hyperkalemic effects associated with RAAS inhibitors as well as beta blockers and potassium sparing diuretics [7].

Managing hyperkalemia can be challenging. Dietary restrictions, diuretics, supplemental bicarbonate and decreasing medications associated with hyperkalemia are often unsuccessful. For many years, Kayexalate (sodium polystyrene sulfonate) has been the only available potassium-binding agent. Unfortunately, the potassium-lowering effects of Kayexalate are delayed and often unreliable, and detrimental but well-described side effects have been reported [8]. Loop diuretics can be effective and relatively rapid potassium-lowering agents, but they are often ineffective in patients with advanced kidney disease. This paucity of effective drugs has shed a light on the critical need for new medications to treat hyperkalemia.

Two new potassium-lowering agents have generated considerable excitement in the medical field. The first agent, patiromer, is a nonabsorbed cation exchange polymer that binds potassium in the gastrointestinal tract, increasing fecal potassium excretion and thereby lowering serum potassium levels [9]. The second agent, zirconium cyclosilicate, also binds gastrointestinal potassium but via an insoluble crystalline lattice structure, which selectively exchanges potassium for sodium and hydrogen [10].

A multinational, single-blind, two-phase study by Weir and colleagues included 234 patients with stage 3 or 4 chronic kidney disease (estimated glomerular filtration rate [eGFR] of 15 to <60 ml per minute per 1.73 m^2 of body-surface area). Patients had been receiving stable doses of one or more RAAS inhibitors for at least 28 days, and their serum potassium ranged between 5.1 and 6.5 mEq/l [9]. All patients received a patiromer dose of 4.2 to 8.4 gram twice a week, and 75% achieved potassium levels of 3.8 to less than 5.1 mEq/l by the end of 4 weeks. Of those that achieved serum potassium reduction, 107 were then randomized to maintenance patiromer or an 8-week placebo-controlled withdrawal phase. Recurrent hyperkalemia (potassium ≥5.5 mEq/l) developed rapidly and more frequently with placebo (60% incidence *vs.* 15% with continued patiromer). Constipation was the most common side effect (11%). Given the study duration of only 12 weeks, potential adverse effects with long-term use of patiromer remain unclear; however, a separate open-label trial noted fairly modest side effects (hypomagnesemia, hypokalemia and constipation) in 306 patients taking patiromer for one year [11]. Despite its apparent effectiveness and tolerability, serum potassium levels decline gradually, which suggests using patiromer for severe hyperkalemia in the acute setting would be unwise if it were to delay initiation of more rapid and effective treatments.

A two-phase, double-blind study of zirconium cyclosilicate enrolled 753 patients with hyperkalemia, of which 75% had eGFR less than 60 ml per minute per 1.73 m^2, 60% had diabetes and 40% had heart failure [10]. Patients were randomly assigned to receive the drug

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at 1.25, 2.5, 5 and 10 g three times a day for 48 hours. Those achieving normal serum potassium levels at 48 hours were randomly assigned to zirconium cyclosilicate or placebo once daily from day 3 to 14. Potassium decreased from an overall baseline of 5.3 mEq/l to 4.9, 4.8 and 4.6 mEq/l with study drug doses of 2.5, 5 and 10 g, respectively (p-value <0.001 in all groups) compared with reductions to only 5.1 mEq/l in the 1.25-g group and the placebo group. Patients on the 5 and 10-g dose maintained serum potassium at 4.7 and 4.5 mEq/l, respectively throughout the two-week study period compared with more than 5 mEq/l in the placebo group.

These studies provide some promising insight into therapy for hyperkalemia and potential medication alternatives for patients with indications for RAAS inhibition but difficult-to-control serum potassium levels or potentially even in in patients awaiting dialysis access maturation but needing temporizing measures for mild to moderate hyperkalemia. Neither patiromer nor zirconium cyclosilicate has been studied in patients with serum potassium above 6.5 mEq/l, those with electrocardiogram findings of hyperkalemia, or even in hospitalized patients. These studies are still limited in terms of follow up (up to one year for patiromer) and overall mortality outcomes. More studies are needed to further explore the use of these medications in patients at even greater risk for hyperkalemia and its complications. Nevertheless, patiromer and zirconium cyclosilicate offer potential for concomitant use with hyperkalemia-inducing RAAS inhibitors in hopes of extending their renoprotective and cardioprotective effects for our highest-risk patients.

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