New Options for Treating Hyperkalemia in 2016

By Edgar V. Lerma

P
tients and physicians have new choices for treating hyperkalemia in 2016. The FDA recently approved patiromer calcium sorbix (Relypsa, Redwood City, CA) this year. Recent approval of the new heart failure medication EntrestoTM (LCZ696; sacubitril/valsartan) has reinvigorated an interest in the health care community to optimize treatment regimens that include life-saving therapies such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs). These agents belong to a larger category of drugs known as renin-aldosterone-angiotensin system (RAAS) inhibitors, and are known in some patients to increase serum potassium to dangerously high levels that can lead to life-threatening arrhythmias. Patients who have chronic kidney disease (CKD), advanced age, heart failure, and/or diabetes mellitus are particularly prone to developing hyperkalemia. Within the nephrology community, hyperkalemia has been reported in over half of all CKD patients (1). The onset of hyperkalemia, or fear thereof, may lead to discontinuation or suboptimal dosing of RAAS inhibitors in patients who could really benefit. Current therapies for the acute and chronic management of hyperkalemia include sodium polystyrene sulfonate (SPS; Kayexalate), a nonspecific cation exchange resin, and are known in some patients to increase serum potassium to dangerously high levels that can lead to life-threatening arrhythmias. Patients who have chronic kidney disease (CKD), advanced age, heart failure, and/or diabetes mellitus are particularly prone to developing hyperkalemia. Within the nephrology community, hyperkalemia has been reported in over half of all CKD patients (1). The onset of hyperkalemia, or fear thereof, may lead to discontinuation or suboptimal dosing of RAAS inhibitors in patients who could really benefit.

Current therapies for the acute and chronic management of hyperkalemia include sodium polystyrene sulfonate (SPS; Kayexalate), a nonspecific cation exchange resin that may (or may not) provide temporary alleviation, but is fraught with serious gastrointestinal toxicities and undesirable binding to Mg2+ and Ca2+ and exchange with sodium. Other therapies, such as intravenous insulin and dextrose, sodium bicarbonate, or diuretics, provide only temporary relief in the emergent clinical setting, and strict regulation of dietary intake of potassium is difficult to enforce. Although dialysis can be effective, it is an invasive and expensive option, and potentially may be avoided now that new, orally administered, potassium reducing agents are on the horizon. ZS-9 is an inorganic, non-absorbed, selective potassium ion trap that has 9 times the potassium-binding capacity of SPS and 125-fold selectivity for potassium over calcium and magnesium, compared with SPS. ZS-9 rapidly normalized serum potassium levels in patients with hyperkalemia in two double-blind, placebo-controlled, Phase 3 studies. ZS Pharma recently announced acceptance by FDA of a New Drug Application for ZS-9 for the treatment of hyperkalemia. The anticipated Prescription Drug User Fee Act (PDUFA) decision date is May 26, 2016. ZS-9 has demonstrated acute and sustained potassium-lowering properties, with low rates of adverse events and no significant impact on other electrolytes in >1000 patients with hyperkalemia. ZS-9 activity was consistent across all patients, regardless of presence or absence of comorbidities, including CKD stage 4 or 5 and the use of RAAS inhibitors. In urgent treatment of severe hyperkalemia (serum potassium greater than 6 mEq/L), pooled analysis of the two phase 3 studies showed that treatment with a single 10 gram dose of ZS-9 lowered potassium as early as 1 hour after administration. Studies have shown that ZS-9 achieves and maintains normokalemia for up to 28 days with a safety profile comparable to placebo. Additional studies are ongoing to demonstrate the long-term efficacy and safety of ZS-9. Concerns regarding exchange of sodium to cause edema seem minor, but will be monitored.

The organic polymer resin patiromer calcium sorbitex (patiromer) has also shown potential to treat hyperkalemia where immediate responses are not required. Studies on patiromer were predominantly observational, with only a placebo-controlled trial of short-term maintenance of normokalemia in CKD patients maintained on RAAS. There is also a somewhat limited demographic profile, as these studies have mostly been conducted on white patients from Eastern Europe. In addition, patiromer releases calcium and binds to not only potassium but magnesium as well, resulting in hypomagnesemia in some patients. Nonetheless, it appears to be largely well tolerated and effective in the treatment of hyperkalemia in individuals with advanced CKD, those with congestive heart failure, and in diabetics.

If approved, ZS-9 will represent another promising new therapy for both the acute and chronic management of hyperkalemia. This innovative therapy warrants close attention for an FDA decision in 2016, and availability in the clinic shortly thereafter. We will then learn exactly where these new agents fit in for the care of patients.

Reference

Suggested Reading

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