Hyperkalemia

Achieving Normal Potassium Levels in Heart Failure, Chronic Kidney Disease, Diabetes Mellitus (DM) Patients

Chicago, IL., April 2, 2016 – Hyperkalemia, defined as a reduction in serum potassium [K+] of ≥5.1 mEq/L, is a common electrolyte disorder found in patients with heart failure (HF), chronic kidney disease (CKD), diabetes mellitus (DM), and those receiving renin-angiotensin-aldosterone system (RAAS) inhibitors. The condition has been associated with neuromuscular complications including paresthesias and fasciculations in the extremities. It has also been associated with cardiac complications, in particular electrocardiography (ECG), which may include peaked T waves, ST-segment depression, widening of the QRS and PR intervals, and loss of the P wave. The appearance of a sine-wave pattern may indicate impending ventricular fibrillation and asystole in these patients. In many instances the ECG changes are also accompanied by parallel abnormalities of other serum electrolytes such as sodium and calcium.

“Hyperkalemia remains one of the major reasons for sub-optimal RAASi therapy in patients with heart failure. Until now we have not had good options for the long term management of chronic hyperkalemia. These data are exciting. Now along with the potential for acute treatment, we may be able to use this agent for chronic therapy as well as optimizing RAASi therapy.” Javed Butler MD, MPH, Division Chief of Cardiology, Professor in the Department of Medicine, and Co-Director of the Heart Institute at Stony Brook School of Medicine in Stony Brook, NY.

To assess the onset-of-rapid potassium reduction by sodium zirconium cyclosilicate (ZS-9) across patient subgroups stratified by race, age, and comorbidities, researchers conducted a subgroup analysis of the Hyperkalemia Randomized Intervention Multidose ZS-9 Maintenance (HARMONIZE) trial data.

During the induction phase of this trial, patients received 10g of ZS-9 three times a day for 48 hours. Those patients who achieved normal serum potassium levels, defined as 3.5-5.0 mEq/L, were then randomized to receive a daily dose of 5g, 10g, or 15g of ZS-9 or placebo for 28 days. The researchers stratified the patients by race, age, renal function, comorbidities, and RAAS inhibitor use. The data showed that the median time to normalization across the subgroups was 2.0-2.3 hours. Some 82-90% of the individuals achieved a normal serum potassium levels within 24 hours and 91-99% achieved normal serum potassium levels within 48 hours. The data showed:

<table>
<thead>
<tr>
<th>Heart Failure Patients (N =)</th>
<th>Chronic Kidney Disease Patients</th>
<th>Diabetes Mellitus Patients</th>
<th>Patients Utilizing RAAS Inhibitors</th>
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</thead>
</table>


The most common adverse effects (AEs) were gastrointestinal (GI) disorders. GI events accounted for 5 of 10 AEs in HF, 7 of 13 AEs in CKD, 8 of 16 AEs in Diabetes, and 6 of 12 AEs in the patients receiving RAAS inhibitor therapy.

Sodium zirconium cyclosilicate (ZS-9) is an insoluble, non-absorbed zirconium silicate that captures potassium ions. The potassium selectivity of ZS-9 enables high in-vitro binding capacity for potassium ions even in the presence of other competing ions. This medication is an investigational product that is not approved by the U.S. Food and Drug Administration (FDA) or European regulatory agencies.

The Hyperkalemia Randomized Intervention Multidose ZS-9 Maintenance (HARMONIZE) trial was a prospective, randomized, double-blind, placebo-controlled trial of 258 patients with CKD, HF, diabetes, and those on RAAS inhibitor therapy. The trial included an open-label induction phase in which patients received 10g of ZS-9 administered three times daily for 48 hours and were monitored to establish the speed and magnitude of serum potassium changes. The patients who achieved normal potassium levels were randomized in a double-blind fashion to one of three doses of ZS-9 (5g, 10g or 15g) or placebo administered once-daily for 28 days (the randomized withdrawal period). The primary efficacy endpoint compared the mean serum potassium levels of each ZS-9 treatment group to that of placebo over the interval between day 8 and day 28 of the randomized withdrawal period.

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