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Treatment of Hyperkalemia with ZS-9, a Novel Potassium Trap, Results in Rapid and Sustained Reduction of Serum Potassium

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Hyperkalemia (excess serum potassium [K⁺]) is a common disorder in patients with heart failure, diabetes and chronic kidney disease and limits use of life-saving renin-angiotensin-aldosterone system (RAAS) therapies, such as ACE inhibitors and ARBs. Current management of hyperkalemia includes a low K⁺ diet or treatment with the non-specific polymer resin, sodium polystyrene sulfonate (SPS), which is poorly tolerated with questionable efficacy. There is an unmet clinical need for a safe and effective treatment that will both enable use of RAAS therapies and liberalize patient diets. Sodium zirconium cyclosilicate (ZS-9) is a novel therapy designed to specifically trap excess K⁺ in the GI tract. In this multicenter, double-blind, placebo-controlled Phase 3 trial, 753 patients with serum K⁺ 5-6.5 mEq/L were randomized to ZS-9 (1.25, 2.5, 5 or 10g) or placebo three times daily (TID) for 48 h. Patients who achieved normal K⁺ (3.5-4.9 mEq/L) at 48 h were re-randomized to the same ZS-9 dose or placebo once daily (QD) for 12 additional days. Efficacy endpoints included rate of K⁺ change over the first 48 h and maintenance of normokalemia through Day 15. Within the initial 48 h, K⁺ was significantly reduced from a mean baseline K⁺ of 5.3 mEq/L by 0.46, 0.54, and 0.73 mEq/L in the 2.5, 5 and 10g dose groups (p<0.001 for each). Normal K⁺ was maintained for 12 days with ZS-9 5g and 10g QD (p<0.008 and p<0.0001, respectively). ZS-9 was well tolerated, with adverse event (AE) rates similar to placebo. These results show ZS-9 TID produced a rapid and acute K⁺ decrease within 48 h in hyperkalemic patients and maintained normal K⁺ when given QD for 12 additional days, with low rates of AEs. ZS-9 may represent a new treatment for hyperkalemia, yielding benefit to patients in whom optimal use of life-saving cardio- and reno-protective RAAS therapies is limited.

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