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Kayexalate and Lokelma For the Management of Hyperkalemia

Introduction

1. Hyperkalemia is defined by a serum or plasma potassium level > 5 mEq/L
2. Elevated potassium (K) levels may present with:
    a. Electrocardiographic (ECG) changes causing life-threatening arrythmias, AND/OR
    b. Muscle weakness or paralysis
3. Hyperkalemia may be caused by increased K intake, intracellular K shifts, or impaired K excretion
4. Neuromuscular weakness, paralysis, or ECG changes with an elevated K > 5.5 mEq/L should be treated aggressively
5. Up to 11% of patients arriving to the emergency department present with hyperkalemia and a mortality rate of 36% with comorbid conditions (heart failure, chronic kidney disease, diabetes)

Pharmacology

	Sodium Polystyrene Sulfonate (Kayexalate)	Sodium Zirconium Cyclosilicate (Lokelma)
Dose	Oral: 15g 1-4 times daily Rectal: 30-50g every 6 hours	Initial: • 10g TID for up to 48 hours • Adjust dose by 5g daily at 1-week intervals Maintenance • 10g once daily • Range: 5g every other day – 15g daily • Max: 15g/day Renal impairment, hemodialysis • 5g – 15g daily on nondialysis days
Administration	• Shake the suspension well or add to non-potassium containing food • Separate oral medications 3 hours before and after	• Empty contents of package into 45mL of water, stir and drink immediately • Separate oral medications 2 hours before and after
MOA	**Potassium Binder** Removes K by exchanging sodium ions for potassium ions in the intestine before the resin is passed from the body	**Potassium Binder** Exchanges K for hydrogen and sodium, reducing concentration of free K in the gastrointestinal lumen, lowering serum K levels
PK/PD	**Onset**: hours to days **Absorption**: None **Excretion**: Feces	**Onset**: 1-4 hours **Absorption**: None **Metabolism**: None **Excretion**: Feces
Adverse Effects	Hypernatremia, hypocalcemia, hypomagnesemia, anorexia, constipation, diarrhea, nausea, vomiting, ischemic colitis and intestinal necrosis	Edema
Drug Interactions	Category X: avoid combination • Laxatives • Meloxicam • Sorbitol	Risk D: consider therapy modification • Clopidogrel • Dabigatran • Warfarin
Warnings	Intestinal necrosis and gastrointestinal events (bleeding, ischemic colitis, perforation), especially in addition to sorbitol	Edema most commonly reported in nondialysis patients with heart failure or sodium-restricted diet
Comments	• Practical exchange ratio is 1 mEq K per 1 gram of resin • Only 33% of sodium content is delivered to the body	• Each 5g dose contains ~400mg sodium

Overview of Evidence

Author, year	Design/ sample size	Intervention & Comparison	Outcome
Lepage 2015	Randomized control trial (n=33)	• Placebo vs sodium polystyrene sulfonate 30g orally daily x 7 days	• Sodium polystyrene sulfonate reduced K greater than placebo (mean difference -1.04 mEq/L) • Average treatment duration **6.9 days** • Trend toward higher rates of electrolyte disturbances and increased GI side effects in treatment group
Fishbane 2019*	Randomized, double blind, placebo controlled trial (n=196)	• Placebo vs sodium zirconium cyclosilicate 5g daily on non-dialysis days (max 15g over 4 week increments)	• 41.2% of patients in sodium zirconium cyclosilicate vs 1.0% of placebo were treatment responders • Rescue therapy to reduce hyperkalemia during treatment period required by 2.1% sodium zirconium cyclosilicate vs 5.1% placebo • Sodium zirconium cyclosilicate required more than **3 hemodialysis treatments** after the interdialytic interval before a reduction in K without rescue therapy
Zannad 2015**	Randomized, double blind, placebo controlled trial (n=258)	• Randomized to sodium zirconium cyclosilicate 5g, 10g, or 15g or placebo: 1 time/day x 28 days	• Sodium zirconium cyclosilicate reduced aldosterone by -31%, -30%, and -30% in the 5g, 10g, and 15g groups, respectively compared to 14% increase in placebo group • Similar results to HARMONIZE trial with median time to serum K normalization of **2 hours**
Scherr 1961	Retrospective review (n=32)	• Sodium-cycle sulfonic polystyrene cation-exchange resin administered orally or by rectum in divided doses totaling 10g-60g per day	• 23 patients showed a decrease in K of at least 0.4 mEq/L in the **first 24 hours** • K change associated with reversion of normal EKG in every case • 2 patients required additional therapy with sodium bicarbonate, glucose, and insulin • Constipation occasionally encountered and controlled with enemas or cathartics
Gruy-Kapral 1998	Prospective controlled trial (n=6)	• Single-dose resin-cathartic vs placebo	• No reduction in serum potassium concentrations at **12 hours**
Kosiborod 2014*	Randomized, double blind, placebo controlled trial (n=258)	• Zirconium cyclosilicate 5g, 10g, 15g, or placebo daily x 28 days	• Median time to normalization was **2.2 hours** • 84% of patients achieved normokalemia by 24 hours and 98% by 48 hours
Peacock 2020	Phase 2 trial (n=70)	• Zirconium cyclosilicate 10g TID or placebo	• Patients treated with SZC experienced a 0.13 mEq/L greater drop in potassium, but this was not statistically significant. • Trend towards more patients treated with SZC achieving a potassium below 6 mE/L • Non-**significant trend towards patients treated with SZC** being less likely to require additional therapies for **hyperkalemia (16% vs. 31%)**
Ash*** 2015	Phase 2 trial (n=54)	• Zirconium cyclosilicate 0.3g, 5g, 10g, or placebo TID	• **At hour 2,** Zirconium cyclosilicate 10 g reduced potassium by 0.13 mE/L compared to 0.02 mEq/L of placebo. • **At hour 8**, Zirconium cyclosilicate 10 g reduced potassium by 0.37 mEq/L compared to 0.24 mEq/L of placebo.
Packham 2015	Phase 3 trial (n=753)	• Zirconium cyclosilicate 1.25g, 2.5g, 5g, 10g, or placebo	• **Over the first four hours, SZC reduces potassium by an average of ~0.2 mEq/L compared to placebo.** • With repeated dosing over the **first 24 hours**, SZC reduces the potassium by an average of 0.4 mEq/L.

Normalization defined as K 3.5 – 5 mEq/L
*Baseline K 5.5 – 5.6 mEq/L
**43% mild hyperkalemia, 45% moderate hyperkalemia, 13% severe hyperkalemia at baseline
*** Baseline K 5.0 – 5.2 mEq/L

Conclusions

1. Sodium zirconium cyclosilicate has improved upon the old standard sodium polystyrene sulfonate through its nonabsorbable dose-dependent potassium lowering.
2. Sodium zirconium cyclosilicate has been shown to reduce K levels quicker than sodium polystyrene sulfonate and may be more beneficial in heart failure and cardiorenal disease via renin-angiotensin-aldosterone system.
3. Sodium polystyrene sulfonate has a variable onset of action (2-12 hours) and a lack of robust efficacy.
4. Sodium zirconium cyclosilicate has a much quicker onset (1-4 hours), with dose dependent pharmacokinetics, however no studies have evaluated the clinical implication on acute hyperkalemia.

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