CKD AND ARRHYTHMIAS: ELECTROLYTE ABNORMALITIES AND POTENTIAL TREATMENTS

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Disclosure of Interests

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Electrolytes for Discussion

Potassium
Magnesium
Mineral Metabolism
Hyperkalemia Is Prevalent Among Older Populations With Advanced Kidney Disease and/or Heart Failure

5-Year Database Prevalence of Hyperkalemia
Control Population vs CKD Stages 3a, 3b, 4 in Patients ≥65 Years

5-Year Database Prevalence of Hyperkalemia
Control Population vs CKD Stages 3-4 + Heart Failure in Patients ≥65 Years

CKD stages are based on estimated glomerular filtration rates (eGFR measured in mL/min/1.73m²)
Stage 3a (eGFR of 45-59), Stage 3b (eGFR of 30-44), Stage 4 (eGFR of 15-29)

Based on analysis of 1.63 million persons aged 5+ years with potassium values on 2 dates (2008-2012), with >1 K⁺ value between 2.5 and 10 mEq/L during 2008-2012.
Control population composed of patients ≥65 years without CKD stages 2-5, heart failure, diabetes, or end-stage renal disease (ESRD).
Hyperkalemia defined as highest reported potassium value ≥5.1 mEq/L in 2008-2012.

Hyperkalemia Contributes to ED Visits, Hospitalizations, and Health Care Costs

- In 2011, the estimated total annual hospital charges for Medicare admissions with hyperkalemia as primary diagnosis were ~$697 million
- Average Medicare LOS was 3.2 days; mean charges of $24,085 per stay
- One-third were discharged to another short-term hospital, institution, or home health care

ED: emergency department; LOS: length of stay.
Adjusted Mortality* by Serum K+ Level in Patients 45 to 64 Years and ≥65 Years With and Without Comorbid Illness

Normal Range

Levels of Serum Potassium (mEq/L)

Increases in mortality remained after adjustments for demographic characteristics and comorbidities

*Evaluated through de-identified medical records (2007-2012) of individuals with ≥2 mEq/L serum K+ readings (Humedica, Cambridge, MA). Spline analyses were performed to assess mortality at 0.1 mEq/L increments of serum K+ after adjusting for covariates and interactions. Comorbid patients are those with diabetes, heart failure, CKD stages 3-5, cardiovascular disease, or hypertension.

Serum Potassium Homeostasis and Regulation

- Increased $K^+$ intake
- Reduced $K^+$ excretion
- $K^+$ movement out of cells

Total body potassium:
- ~98% intracellular
- ~2% extracellular

Normal serum potassium

Increased serum potassium

- Release of insulin
- Release of aldosterone
- Release of catecholamines

Reduction of serum potassium

$K^+$ excretion:
- ~90% renal
- ~10% GI (colon)

Increased cellular uptake

Increased renal excretion

Potassium Absorption and Secretion

- Potassium absorption and secretion occurs in distinct areas of the nephron and gastrointestinal tract

- **Nephron**
  - $\text{K}^+$ reabsorption in the proximal tubule and loop of Henle
  - $\text{K}^+$ secretion in the distal and collecting tubules

- **Gastrointestinal tract**
  - $\text{K}^+$ absorption in the jejunum and ileum (passive)
  - $\text{K}^+$ secretion in the colon (passive and active)
Diabetic Patient with CKD: Many Reasons for Hyperkalemia

Redistribution

Acidosis
Hypertonicity

Drugs
Beta blocker
RAAS blockers

Reduction of
Insulin
Glucocorticoid
Decreased GFR
Many reasons for hyperkalemia

Redistribution
  Acidosis

Drugs
  Beta Blockers
  RAAS Blockers
  Potassium Sparing Diuretics

Reduced
  Decreased GFR
  Pre-renal Azotemia
Treatment Options for Hyperkalemia

- Insulin
- Calcium gluconate salt
- β-adrenoreceptor agonists
- Loop diuretics
- Sodium bicarbonate
- Dialysis
- SPS
- RAASi reduction
- Low K⁺ diet
- Membrane stabilization
- K⁺ redistribution
- K⁺ elimination
- Removal/reduction of drugs that ↑ serum K⁺

Therapy

- Emergent
- Intermediate
- Maintenance

SPS: sodium polystyrene sulfonate.

Potassium and Hemodialysis

• n= 81,013 hemodialysis patients followed for 3 years
• Nine quarterly – averaged pre-dialysis serum K groups (<4.0, ≥ 6.3 mEq/L and seven increments in between) and four dialysate K+ concentration groups created in each of 12 calendar quarters
• Death risk associated with pre-dialysis K level and dialysate K

Hazard ratios of all-cause mortality for predialysis serum K categories in 21,013 incident MHD patients observed for up to 3 yr.

Hazard ratios of all-cause mortality for predialysis serum K categories in 53,206 prevalent MHD patients observed for up to 3 yr.
Three-year crude mortality rates in 16 groups of serum and dialysate K concentrations

Csaba P. Kovesdy et al. CJASN 2007;2:999-1007
Potassium and CKD

- n = 36,359 patients with eGFR < 60 ml/min
- Cleveland Clinic data base
- Age: 71 years
- eGFR= 47.5 ml/min
- DM%: 18%

Relationship between serum potassium (as a continuous measure) and all-cause mortality

**KAYEXALATE (Sodium Polystyrene Sulfonate) Is Indicated for the Treatment of Hyperkalemia**

<table>
<thead>
<tr>
<th>PROPERTY</th>
<th>Kayexalate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of Action</strong></td>
<td>Potassium binder that is ingested and exchanges sodium for potassium in the GI tract to reduce serum potassium levels¹</td>
</tr>
<tr>
<td><strong>Safety and Tolerability</strong></td>
<td>Intestinal necrosis warning, GI side effects¹</td>
</tr>
<tr>
<td><strong>Design/Active Pharmaceutical Ingredient</strong></td>
<td>Bulk gel material, nonuniform size, and fine, brown, clay-like consistency¹²</td>
</tr>
<tr>
<td><strong>Counterion</strong></td>
<td>Na⁺-loaded, about 1/3 is delivered to the body¹</td>
</tr>
<tr>
<td><strong>Efficacy Data</strong></td>
<td>Efficacy and safety not studied in large, systematic, long-term Trials²</td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Average daily adult dose is 15g-60g/day¹</td>
</tr>
</tbody>
</table>

Kayexalate Precaution: Patients Sensitive to Sodium Increase

• Caution is advised when Kayexalate is administered to patients who cannot tolerate even a small increase in sodium loads (ie, severe congestive heart failure, severe hypertension, or marked edema)

• In such instances compensatory restriction of sodium intake from other sources may be indicated

# Limitations of Long-Term Hyperkalemia Management Strategies

## Treatment

### RAASi reduction
- Limiting the dose or discontinuing treatment of drugs known to be effective in these populations

### Kayexalate
- Warnings related to serious gastrointestinal adverse events
- Precaution related to sodium

### Dietary K⁺ restriction of 50-75 mEq/day
- Potassium is common ingredient in many foods
- Restricts consumption of healthy foods (such as the DASH diet)
- Low K⁺ diet often expensive

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Patiromer (RLY5016) is a Polymer That Binds Potassium in the Colon

- Patiromer is a non-absorbed $K^+$ binding polymer
- Patiromer binds $K^+$ in colon (not dietary $K^+$)
- Patiromer acts as a “sink” to increase colonic $K^+$ excretion

Hyperkalemia

Hyperkalemia is most commonly caused by chronic kidney disease (CKD), or the use of RAAS blockade drugs that limit urinary $K^+$ excretion and increase serum $K^+$ level

Buysse JM, et al. 2012 Future Cardiol. 8:17-28
Phase 3, 2-Part CKD Pivotal Study in Hyperkalemia Subjects on RAASi: Under Special Protocol Assessment with FDA

CKD 3/4, on RAASi meds
K = 5.1 - < 6.5

Moderate – to Severe
(5.5 - < 6.5)

Mild (5.1 - < 5.5)

Part A Baseline

Part A Endpoint (4-wk Tx)

Part A, Single-Arm 4-Weeks

Part B, Placebo-Controlled, Randomized Withdrawal 8-Weeks

Part B K⁺ Endpoint (at Week 4)

Change from Baseline in Mean (±SE) Serum K⁺ to Week 52

- All serum K⁺ analyses are based on central lab values; 3 patients (2 in the mild HK group and 1 in the moderate HK group) did not have a central lab serum K⁺ value at baseline and therefore are not included in the analysis at this timepoint. *p<0.001 by t-test for change from baseline. †p<0.001 by t-test for change from Week 52 (or from the last dose of patiromer received during the study). BL, baseline; F/Up, follow-up; HK, hyperkalemia.

Study 205

Secondary Endpoint: Change in Systolic Blood Pressure Over 52 Weeks (Intention to Treat Population)

- Clinically relevant reductions in systolic blood pressure were observed in all starting dose groups in both strata
- The 52 week change in SBP – Stratum 1: -15.7 mmHg, Stratum 2: -17.1 mmHg

SBP = systolic blood pressure
Data on File, Relypsa – 205 CSR
## Most Common Adverse Events Over 52 Weeks*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Mild HK (n=220)</th>
<th>Moderate HK (n=84)</th>
<th>Overall (n=304)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypomagnesemia†</td>
<td>15 (7%)</td>
<td>11 (13%)</td>
<td>26 (9%)</td>
</tr>
<tr>
<td>Worsening of HTN</td>
<td>14 (6%)</td>
<td>10 (12%)</td>
<td>24 (8%)</td>
</tr>
<tr>
<td>Worsening of CKD</td>
<td>14 (6%)</td>
<td>14 (17%)</td>
<td>28 (9%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12 (6%)</td>
<td>5 (6%)</td>
<td>17 (6%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>11 (5%)</td>
<td>8 (10%)</td>
<td>19 (6%)</td>
</tr>
<tr>
<td>Hypoglycemia†</td>
<td>4 (2%)</td>
<td>6 (7%)</td>
<td>10 (3%)</td>
</tr>
</tbody>
</table>

Figure 1. ZS-9: A Novel Selective Potassium Trap

ZS-9 Crystal Structure

Average Width of Micropore Opening 3Å

**ZS-9 PROPERTIES**

- Unique microporous zirconium silicate compound
- Designed to be selective for $K^+$
- Builds on long history of Zr use in dialysis and other biomedical applications
- Insoluble and highly stable
- Non-systemically absorbed
- ZS-9 has 9.3 times more $K^+$ binding capacity than Kayexalate® (SPS)
- ZS-9 is >125 times more selective for $K^+$ than Kayexalate
- Kayexalate is more selective for $Ca^{2+}$ than $K^+$
Predisposition to Hyperkalemia: Impaired Extrarenal Buffering

- Insulin deficiency
- Beta blockers
- Autonomic Insufficiency
- Digoxin

Insulin and β agonists shift potassium into cells
2K⁺

Acidosis, hyperosmolarity, cell lysis shift potassium out of cells

ICF [K⁺] = 140

ECF [K⁺] = 4

KDIGO Controversies Conference on CKD & Arrhythmias
October 27-30, 2016 | Berlin, Germany
Magnesium

- Complex effect on myocardial ion flux
- Obligate CO-factor in all reactions that require ATP
- Essential for activity of Na-K-ATPase
- Low serum magnesium impairs Na-K-ATPase, and limits inward potassium current
- More common in older patients on diuretics or with interstitial kidney disease!
Magnesium Depletion

- Widening of QRS, peak T waves
- Prolongation of PR interval
- APC, PVC, atrial fibrillation, ventricular arrhythmias
- Facilitates digoxin cardiotoxicity (additive effect on intracellular potassium depletion)
Magnesium Depletion

- Increases the risk of torsades des pointes, particularly in people taking class IA or III antiarrhythmic drugs
- Low serum magnesium most concerning with acute myocardial ischemia or infarction
- Mild elevation of serum magnesium protects myocardium from ischemia-reperfusion injury by promoting restoration of high energy phosphates.
Treatment?

- Does magnesium supplementation help?
- Where is the data?
- Under what clinical circumstances is it indicated?
- What about hemodialysis patients? No magnesium in dialysate.
Mineral Metabolism and Mortality

- Decreased survival in dialysis patients with increased serum phosphate, calcium, calcium-phosphate product, and PTH.
- All studies not consistent
- Theory: these mineral bone disease alterations can lead to arterial calcification, accelerated atherosclerosis and increased cardiovascular events and death.
Mineral Metabolism and Mortality

- n = 40,538 hemodialysis patients with at least one measure of phosphorus and calcium in 1997
- Unadjusted, case-mix adjusted and multi-variable adjusted relative risks of death were calculated using proportional hazards regression
- Population attributable risk for disorders of mineral metabolism: 17.5 % (mostly due to hyperphosphatemia)
- Serum phosphate over 5.0 mg/dL and associated with increased risk of death
- PTH concentrations over 600 pg/ml

Unadjusted, case mix–adjusted, and multivariable-adjusted relative risks (RR; of death) and 95% confidence intervals (CI) for eight categories of serum phosphorus (referent range, 4.0 to 5.0 mg/dl).

Geoffrey A. Block et al. JASN 2004;15:2208-2218
Unadjusted, case mix–adjusted, and multivariable-adjusted RR (of death) and 95% CI for eight categories of adjusted serum calcium (measured calcium adjusted for serum albumin, referent range, 9.0 to 9.5 mg/dl).

Geoffrey A. Block et al. JASN 2004;15:2208-2218
Unadjusted, case mix–adjusted, and multivariable-adjusted RR (of death) and 95% CI for 12 categories of calcium × phosphorus product (referent range, 40 to 45 mg²/dL²).

Geoffrey A. Block et al. JASN 2004;15:2208-2218
Unadjusted, case mix–adjusted, and multivariable-adjusted RR (of death) and 95% CI for four categories of intact parathyroid hormone (referent range, 150 to 300 pg/ml).

Geoffrey A. Block et al. JASN 2004;15:2208-2218
Mineral Metabolism and Mortality

- n= 25,588 hemodialysis patients in Dialysis Outcomes and Practice Patterns Study (DOPPS)
- Highest mortality noted for patients with calcium over 10.0 mg/dL, phosphorous over 7.0, and PTH level above 600 pg/ml

Risk of all-cause and cardiovascular mortality associated with categories of baseline serum calcium, phosphorus, and parathyroid hormone (PTH) levels.

Risk of all-cause and cardiovascular mortality associated with categories of baseline serum calcium, phosphorus, and parathyroid hormone (PTH) levels

Survival Predictability of time-varying indicators of mineral metabolism in hemodialysis patients

- n = 58,058 dialysis patients (2001-2003)
- Time dependent Cox Models with repeated measures and fixed-covariate Cox Models with only baseline values
- Hypercalcemia and hyperphosphatemia were robust predictors in all models
- Association between serum calcium mortality was different in time-varying models
- Changes in baseline serum calcium and phosphorous levels beyond the K/DOQI recommended targets were associated with increased mortality

Association between albumin-adjusted serum calcium values and the relative risk of death in 58,058 MHD patients over a 2-year interval (July 2001–June 2003) using fixed-covariate Cox modeling with only baseline values (upper panel) and time-dependent Cox models with time-varying repeated measures (lower panel).
Association between the time-varying serum phosphorus values and the relative risk of death in 58,058 MHD patients over a 2-year interval (July 2001–June 2003) using fixed-covariate Cox modeling with only baseline values (upper panel) and time-dependent Cox models with time-varying repeated measures (lower panel).

Association between the time-varying product of serum calcium and phosphorus values and the relative risk of death in 58,058 MHD patients over a 2-year interval (July 2001–June 2003) using fixed-covariate Cox modeling with only baseline values (upper panel) and time-dependent Cox models with time-varying repeated measures (lower panel).

Association between the time-varying serum intact PTH values and the relative risk of death in 58,058 MHD patients over a 2-year interval (July 2001–June 2003) using fixed-covariate Cox modeling with only baseline values (upper panel) and time-dependent Cox models with time-varying repeated measures (lower panel).

Mineral Metabolism and Mortality

- Other studies indicate that low PTH and calcium levels associated with either no effect or increased mortality
- Why the difference?
  Explanations: variations in study design, differences in populations, use of only single measures of serum samples.

Covica A. et al. NDT 2009; 24: 1506.
Mineral Metabolism and Mortality

- No successful interventional trials
- Directionality
- How early should you start treatment?
- What is the target?
- Is there a preferred treatment?
Conclusions

- Treatment of disorders (high and low) of potassium, magnesium, and mineral metabolism may prove to be important in CKD and in ESRD
- We lack evidence from interventional trials
- We lack mechanistic explanations of benefit
- How early should we treat (pre-emptive)?
- What is the target?
- Is there a preferred therapy?