Shedding ‘Lyte on New Agents for the Treatment of Hyperkalemia

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PGY2 Pharmacotherapy Resident
Pharmacy Grand Rounds
February 7, 2017
Objectives

- Describe the pathophysiology of hyperkalemia
- Review current management of hyperkalemia and limitations to current therapies
- Evaluate the role of new agents in the treatment of hyperkalemia
Risk Factors

- Chronic kidney disease (CKD)
  - Cardiovascular disease
  - Diabetes (DM)
- Medications
- Elevated baseline potassium level > 4.5 mEq/L
- Older age

Pathophysiology

- Loss of nephron function
  - CKD
- Decreased renin secretion
  - Renin inhibitor
  - ACEi
  - ARB
- Mineralocorticoid receptor antagonism
  - Aldosterone antagonist

ACEi: angiotensin-converting-enzyme inhibitor
ARB: angiotensin II receptor blocker

McCullough PA et al. Rev Cardiovasc Med. 2015;16(2):140-55
http://www.mayoclinic.org/kidney-cross-section/img-20005978
Pathophysiology

- 5-10% colonic K⁺ excretion
- Upregulation of BK channels in the colon

BK: big potassium channels

• Treatment is indicated:
  • Moderate-severe hyperkalemia
  • EKG changes
Consequences of Hyperkalemia

- Arrhythmias
- All-cause mortality
- Limits treatment optimization for comorbid conditions
  - CKD
  - DM
  - HF

CKD: chronic kidney disease
DM: diabetes mellitus
HF: heart failure

Question #1

• Which of the following is the primary risk factor for hyperkalemia?
  • Renal impairment
  • Hepatic impairment
  • ACE inhibitor use
  • Cardiovascular disease
Treatment Goals

**Acute**
- Shift potassium intracellularly
- Decrease risk of life-threatening arrhythmia

**Chronic**
- Decrease total body potassium
  - Reduce dietary intake
  - Increase excretion (urinary and fecal)
  - Dialysis
  - Medication titration and discontinuation

Pham AQ et al. *J Pharm Practice*. 2016. epub
# Acute Management of Hyperkalemia

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism</th>
<th>Onset</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium gluconate</td>
<td>Stabilize cardiac membrane</td>
<td>1-3 minutes</td>
<td>Short duration of action</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Extravasation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No effect on serum potassium</td>
</tr>
<tr>
<td>Insulin/dextrose</td>
<td>Shift K⁺ into cells</td>
<td>30 minutes</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>B-agonist (albuterol)</td>
<td>Shift K⁺ into cells</td>
<td>30 minutes</td>
<td>Short duration of action</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inconsistent effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Use with caution in ischemic heart disease</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>Shift K⁺ into cells by increasing pH</td>
<td>30 minutes</td>
<td>Risk of volume overload</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Risk of metabolic alkalosis</td>
</tr>
</tbody>
</table>

Pham AQ et al. *J Pharm Practice*. 2016. epub
## Acute/Chronic Management

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism</th>
<th>Onset</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loop diuretics</td>
<td>Increases urinary excretion of K⁺</td>
<td>5-15 minutes</td>
<td>Intravascular depletion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Electrolyte abnormalities</td>
</tr>
<tr>
<td>SPS (Kayexalate)</td>
<td>Resin that exchanges Na⁺ for K⁺, increases fecal elimination</td>
<td>1 hour</td>
<td>Bowel obstruction</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intestinal necrosis</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>Removes K⁺ from plasma</td>
<td>Immediate</td>
<td>Invasive</td>
</tr>
</tbody>
</table>

SPS: sodium polystyrene sulfonate

Pham AQ et al. *J Pharm Practice.* 2016. epub
Sodium Polystyrene Sulfonate (SPS)

1958: FDA approval

1961: Reports of intestinal impaction; FDA recommends to administer with sorbitol (70%)

1962: Kefauver Harris Amendment

1982: Premade SPS suspension in sorbitol

2005: Reports of bowel necrosis (oral and enema) with SPS/70% sorbitol

2005: FDA requires formulation of SPS with 33% sorbitol

2009: Report of 11 cases of SPS-related intestinal necrosis (single center); FDA recommends against sorbitol co-administration

SPS Safety Concerns

- Risk of bowel obstruction
- Risk of intestinal necrosis with sorbitol
  - FDA warning (2009)
- Sodium load
- Drug-drug interactions
  - Must separate by at least 6 hours
- Lack of long-term studies

Question #2

• Which drug-adverse event combination is NOT correct?
  • Calcium gluconate: extravasation
  • SPS: intestinal necrosis
  • Beta-agonists: bradycardia
  • Diuretics: intravascular depletion
Potassium Paradox

• RAAS inhibition reduces blood pressure and end-organ damage from
  • Hypertension
  • Diabetes
  • Heart failure

• Patients with risk factors for hyperkalemia may receive the greatest benefit from RAAS inhibition

Hospital Admission Rates for Hyperkalemia

Patiromer Sorbitex Calcium

- Cross-linked synthetic polymer
  - Exchanges Ca$^{2+}$ for K$^{+}$ in the GI tract, primarily the colon
- Advantages (compared with SPS)
  - Calcium counter-ion
  - Low swelling ratio
  - Binds 8.5 mEq K$^{+}$ per gram
  - Significantly less sorbitol

Vu BN et al. *Cardiol Rev.* 2016;24(6):316-323
Patiromer Clinical Trials

**PEARL-HF**
- Phase 2
- Chronic HF

**AMETHYST-DN**
- Phase 2, dose-finding
- HTN and diabetic nephropathy

**OPAL-HK**
- Phase 3
- CKD

## OPAL-HK

<table>
<thead>
<tr>
<th>Objective</th>
<th>Evaluate safety and efficacy of patiromer in patients with CKD on RAASi therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Phase III, multicenter, randomized, placebo-controlled trial</td>
</tr>
</tbody>
</table>
| Inclusion       | CKD Stage 3 or 4  
K⁺ 5.1-6.4 mEq/L  
RAASi for at least 28 days |
| Exclusion       | K⁺-related EKG changes  
Severe GI disorders  
Kidney/heart transplant  
Recent ACS/stroke/TIA |
| Endpoints       | Phase 1: Mean change in K⁺ from baseline to week 4  
Phase 2: Median change in K⁺ from end of Phase 1 (week 4) to week 8 |

### Study Design

#### Phase 1: Initial treatment (n=243)

<table>
<thead>
<tr>
<th>Mild (5.1-5.5 mEq/L): patiromer 4.2 g BID</th>
<th>(n=92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate-severe (5.5-6.4 mEq/L): patiromer 8.4 g BID</td>
<td>(n=141)</td>
</tr>
</tbody>
</table>

#### Phase 2: Randomized withdrawal (n=107)

Inclusion: Serum $K^+$ ≥ 5.5 mEq/L at baseline and 3.8-5.0 mEq/L at the end of Phase 1

- Placebo group (n=52)
- Patiromer group (n=55)

## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Initial Treatment Phase (n=243)</th>
<th>Randomized withdrawal phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Placebo (n=52)</td>
</tr>
<tr>
<td>Male, %</td>
<td>58</td>
<td>58</td>
</tr>
<tr>
<td>Age, years</td>
<td>64.2</td>
<td>65.0</td>
</tr>
<tr>
<td>T2DM, %</td>
<td>57</td>
<td>63</td>
</tr>
<tr>
<td>eGFR, mL/min</td>
<td>35.4</td>
<td>39.0</td>
</tr>
<tr>
<td>RAASi, %</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>ACEi, %</td>
<td>70</td>
<td>73</td>
</tr>
<tr>
<td>ARB, %</td>
<td>38</td>
<td>31</td>
</tr>
<tr>
<td>Receiving maximal dose, %</td>
<td>44</td>
<td>40</td>
</tr>
</tbody>
</table>

## Results

### Phase 1: Initial treatment (n=243)

<table>
<thead>
<tr>
<th>Mild (5.1-5.5): 4.2 g BID</th>
<th>Reduction in K⁺ from baseline to week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-0.65 mEq/L (-0.74 to -0.55)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate-severe (5.5-6.4): 8.4 g BID</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-1.23 mEq/L (-1.31 to -1.16)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Overall</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-1.01 mEq/L ( -1.07 to -0.55, p &lt; 0.001)</td>
</tr>
</tbody>
</table>

### Phase 2: Randomized withdrawal (n=107)

<table>
<thead>
<tr>
<th>Placebo group</th>
<th>Reduction in K⁺ from the end of Phase 1 to week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+0.72 mEq/L</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patiromer group</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.0 mEq/L</td>
</tr>
</tbody>
</table>

| Between-group difference | +0.72 (95% CI 0.46 to 0.99, p < 0.001) |

Conclusion

• Strengths
  • Patient population
  • Wide range of serum K⁺ levels

• Limitations
  • No placebo/active control in the initial phase

• Conclusion
  • Patiromer reduced K⁺ levels and maintained normokalemia in patients with CKD on RAAS inhibitor therapy

# Patiromer Safety

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Patiromer (n=660)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>7.6%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4.5%</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.5%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.3%</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>4.5%</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>7.1%</td>
</tr>
</tbody>
</table>

Patiromer Dosing and Administration

- Approved October 2015
- Initial dose: 8.4 g daily
  - Titrate by 8.4 g /day at 1-week intervals
- Separate from other medications by at least 3 hours

http://www.relypsa.com/newsroom/digital-library/
Role in Clinical Practice

- Chronic management of hyperkalemia
  - Comorbid CKD, DM, HF
  - RAASi and AA
- Monitor serum potassium and magnesium

AA: aldosterone antagonist
Sodium Zirconium Cyclosilicate (ZS-9)

- Crystalline lattice structure selectively attracts potassium
- Exchanges potassium for sodium and hydrogen counter-ions within entire GI tract
- Awaiting FDA approval

## HARMONIZE Trial

<table>
<thead>
<tr>
<th><strong>Objective</strong></th>
<th>Evaluate safety and efficacy of ZS-9 for hyperkalemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Phase III, multicenter, randomized, placebo-controlled trial</td>
</tr>
</tbody>
</table>
| **Intervention** | Open-label phase  
ZS-9 10 g TID with meals x 48 hours  
Randomized, double-blind phase  
ZS-9 5 g, 10 g, 15 g, or placebo daily x 28 days |
| **Inclusion** | Outpatient  
Hyperkalemia (2 consecutive K⁺ levels ≥ 5.1 mEq/L) |
| **Exclusion** | Dialysis, cardiac arrhythmias |
| **Endpoint** | Primary: comparison of mean K⁺ levels between placebo and each treatment group during days 8-29 |

Kosiborod M et al. JAMA. 2014;312(21):2223-33
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>Open-label phase</th>
<th>Randomized Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ZS-9 10 g TID (n=258)</td>
<td>Placebo (n=85)</td>
</tr>
<tr>
<td>Age, years</td>
<td>64.0</td>
<td>64.3</td>
</tr>
<tr>
<td>Male, %</td>
<td>57.8</td>
<td>51.8</td>
</tr>
<tr>
<td>Serum K+, mEq/L</td>
<td>5.6</td>
<td>4.6</td>
</tr>
<tr>
<td>eGFR, mL/min</td>
<td>46.3</td>
<td>48.0</td>
</tr>
<tr>
<td>RAASi, %</td>
<td>69.8</td>
<td>71.8</td>
</tr>
<tr>
<td>CKD, %</td>
<td>65.5</td>
<td>58.8</td>
</tr>
<tr>
<td>HF, %</td>
<td>36.4</td>
<td>30.6</td>
</tr>
</tbody>
</table>

Kosiborod M et al. JAMA. 2014;312(21):2223-33
# Initial Phase Results

<table>
<thead>
<tr>
<th>Time after dose, hours</th>
<th>Change in K⁺ from baseline, mEq/L</th>
<th>95% CI (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-0.2</td>
<td>-0.3 to -0.2 (p&lt; 0.001)</td>
</tr>
<tr>
<td>2</td>
<td>-0.4</td>
<td>-0.5 to -0.4 (p&lt;0.001)</td>
</tr>
<tr>
<td>4</td>
<td>-0.5</td>
<td>-0.6 to -0.5 (p&lt; 0.001)</td>
</tr>
<tr>
<td>24</td>
<td>-0.7</td>
<td>-0.7 to -0.6 (p&lt;0.001)</td>
</tr>
<tr>
<td>48</td>
<td>-1.1</td>
<td>-1.1 to -1.0 (p&lt;0.001)</td>
</tr>
</tbody>
</table>

- **Normokalemia at 24 hours**: 84% 95% CI, 79-88%
- **Normokalemia at 48 hours**: 98% 95% CI, 96-99%
- **Median time to normokalemia**: 2.2 hours IQR 1.0-22.3 hours

Kosiborod M et al. JAMA. 2014;312(21):2223-33
Randomization Phase Results

Kosiborod M et al. JAMA. 2014;312(21):2223-33

p<0.001 for each ZS-9 dose compared with placebo
Conclusions

• Limitations
  • Outpatient population
  • Clinical outcomes not evaluated

• Conclusions
  • ZS-9 reduced serum K⁺ levels within 48 hours among outpatients with hyperkalemia
  • Daily administration of ZS-9 maintained normokalemia for 28 days

Kosiborod M et al. JAMA. 2014;312(21):2223-33
# ZS-9 Safety

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>ZS-9 (n=1393)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>1.1%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1.6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.9%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.7%</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>0.9%</td>
</tr>
<tr>
<td>Edema</td>
<td>0.9%</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
ZS-9 Role in Clinical Practice

- Chronic management of hyperkalemia
  - Comorbid CKD, DM, HF
  - RAASi

- Potential role in acute management of hyperkalemia
  - 1 hour onset of action
Limitations of New Agents

- Lack of head-to-head trials
- Not evaluated for patients in the ED, inpatient, or ICU
- Not evaluated in patients with AKI or on dialysis
- Additional routes of administration (gastric tube, rectal) not explored
- Limited safety data
Patient Case

HK is a 65 year old female and has a past medical history of T2DM, HTN, and CKD. She takes lisinopril 40 mg daily and metformin 1000 mg twice daily. Her outpatient lab work returns with a serum potassium level of 5.5 mEq/L.
Question #3

• Which initial dose and frequency of patiromer would you recommend to manage her hyperkalemia?
  • Patiromer 8.6 g daily
  • Patiromer 8.6 g twice daily
  • Patiromer 16.8 g daily
  • Patiromer 16.8 g twice daily
Conclusion

• CKD, RAASi, and AA increase the risk of hyperkalemia

• Current therapies do not offer a solution for long-term management of hyperkalemia and are associated with adverse effects

• New potassium binding agents offer a promising role, particularly in patients with CKD, DM, and HF
Cost

- **SPS**
  - 15 g/60 mL (473 mL) = $53.23
    - 30g/120 mL dose = $13.50

- **Patiromer**
  - 8.4 g (#30) = $621.51 ($20.72/dose)
  - 16.8 g (#30) = $621.51
  - 25.2 g (#30) = $621.51
Questions & Discussion