CURRENT EVIDENCE & FUTURE PERSPECTIVES IN NON-DIETARY MANAGEMENT OF CHRONIC HYPERKALEMIA

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OUTLINE

1) Front Matter
2) Diuretics
3) Dose reductions
4) Cation binders
5) Themes and take home messages
Focus on ambulatory (non-emergent) hyperkalemia

Clinical practice = Predicted Evidence-base

- Anecdotal
- "Sood-o Science"
- Diuretics (non-K sparing)
- Dose-reductions
- Oral binders
Diuretics

Efficacy or adverse events RCTs/observational studies on treatment for chronic hyperkalemia: none

Studies on potassium lowering: indirect (HTN trials, acute CHF)
Non-loop diuretics (indapamide, HCTZ, chlorthalidone): no difference
Differing loop diuretic regiments (infusion vs bolus iv): no difference
Absolute effect on K and dose response
SHEP: post-hoc analysis: chlorthalidone 12.5 vs 25: -0.3 mmol/L in K at 3 years

HCTZ vs chlorthalidone

Roush et al HTN, 2015, 65:1041-1046
Alqathani et al, JCC, 2014, 29(1)
Savage et al, Arch Intern Med, 1998, 158
Ernst et al, Amer J HTN, 2010, 23
n=69, 426, new ACE/ARB users; risk factors for hyperkalemia

DM, 7% CHF, 9% CKD, 4% K sparing diuretics, 22% other diuretics
Dose reductions:

Efficacy or AE RCTs on treatment for chronic hyperkalemia: none

• 3 observational studies (2 very small)

Lee et al. J RAAS. 2014, 15(4)

POPULATION: Retrospective; 258 pts; CKD stage 3/4 + RAS + hyper K(≥5.5)

INTERVENTION: i) stop RAS, ii) decrease RAS, iii) continue RAS + treat K(not specified)

OUTCOME: recurrence of hyperK, 2x SCr OR ESKD

Average patient: 61.8 years, eGFR 29, DM 46%, Serum K 5.8

RESULTS:

150 /258 (58.1%) maintained; 41 /150 (27.3%) reduced

108/258 (41.9%) discontinued

RENAL: 41% in maintenance, 63% in withdrawal (total =129 events); HR 1.35 95%CI 1.08-1.92

HyperK: 0.58 in maintenance, 0.47 in withdrawal (pt-yr, NS); no diff in hosp, mortality, BP
## Binders: SPS, Patiromer, ZS-9

Beccari & Meaney, Core Evidence, 2017:12:11-24

### Table 1 Pharmacologic comparison of potassium-lowering agents

<table>
<thead>
<tr>
<th>Pharmacologic property</th>
<th>Sodium polystyrene sulfonate (SPS)</th>
<th>Patiromer calcium sorbitex</th>
<th>Sodium zirconium cyclosilicate(^{18,23-25})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand name</td>
<td>Kayexalate</td>
<td>Veltassa</td>
<td>Lokelma: FDA approved Spring 2018</td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>Binds potassium in the gastrointestinal tract and facilitates excretion in the feces</td>
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<td>Binds potassium in the gastrointestinal tract and facilitates excretion in the feces</td>
</tr>
<tr>
<td>Selectivity for potassium ion</td>
<td>Nonselective; also binds calcium and magnesium</td>
<td>Selective; also binds magnesium</td>
<td>Highly selective; nine times the potassium-binding capacity compared to SPS; also binds ammonium</td>
</tr>
<tr>
<td>Sodium content</td>
<td>1,500 mg sodium per 15 g dose</td>
<td>No sodium content</td>
<td>Approximately 1,000 mg sodium per 10 g dose</td>
</tr>
<tr>
<td>Sorbitol content</td>
<td>20 g sorbitol per 15 g dose</td>
<td>4 g sorbitol per 8.4 g dose</td>
<td>No sorbitol content</td>
</tr>
<tr>
<td>Onset of effect</td>
<td>Variable; 2–6 hours</td>
<td>7–48 hours</td>
<td>1–6 hours</td>
</tr>
<tr>
<td>Duration of effect</td>
<td>Variable; 6–24 hours</td>
<td>12–24 hours</td>
<td>Unclear; appears to be 4–12 hours based on trial data</td>
</tr>
</tbody>
</table>
SPS: Efficacy

- over 5 million doses administered in US annually
- Small physiological studies: variable stool excretion of K
- 3 small RCTs on efficacy; 2 summarized

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Population</th>
<th>Comparator</th>
<th>Outcome</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lepage et al</td>
<td>33</td>
<td>CKD (mean eGFR 20); age 72; 50% on diuretics</td>
<td>Placebo</td>
<td>7 day</td>
<td>SPS: 5.3 (SD 0.2) to 4.0 (SD0.6) P: 5.2 (SD 0.2) to 5.0 (SD 0.3)</td>
</tr>
<tr>
<td>Nasir et al</td>
<td>97</td>
<td>CKD (SC &gt; 132) (no table 1); age 53</td>
<td>Calcium polystyrene sulfonate</td>
<td>3 day</td>
<td>SPS: 5.8 (SD 0.6) to 4.3 (SD 0.6) CPS: 5.8 (SD 0.3) to 4.8 (SD 0.5)</td>
</tr>
</tbody>
</table>

Lepage et al CJASN 2017, 10
Nasir et al J Ayub Med Coll 2014, 26(1)
SPS: adverse events

- Multiple case reports of colonic necrosis/GI injury with 70% sorbitol
- FDA Black box warning in 2009
- Case reports of injury with SPS (- sorbitol) continue
- 2 RCTs: no serious AE (SPS vs CPS no difference; SPS vs placebo more AEs)
- Post marketing surveillance study: large observational study for serious AEs

SPS: Association with colonic necrosis

AJKD
Original Investigation

Association of Prescription of Oral Sodium Polystyrene Sulfonate With Sorbitol in an Inpatient Setting With Colonic Necrosis: A Retrospective Cohort Study

Maura A. Watson, DO, MPH, Thomas P. Baker, MD, Annie Nguyen, PharmD, Mary E. Sebastianelli, RN, Heather L. Stewart, MS, David K. Oliver, RN, Kevin C. Abbott, MD, MPH, and Christina M. Yuan, MD


- Single centre; inpatient; SPS + sorbitol;
- Receipt of SPS prescription vs non-SPS prescription
- Tissue confirmed colonic necrosis; ≤ 30 days after SPS
- SPS 2194 pts vs 123,391 no SPS
- Colonic necrosis in 82 (3 with SPS)
- Incidence rate 0.14% vs 0.07% (RR 2.10 95%CI 0.68-6.48)
- Conclusions: rare; no association
Newer oral binders

- mean change from baseline in serum K (FDA accepted surrogate endpoint)

Palaka et al, Int J Clin Pract. 2018; 72; e13052
### Patiromer (RLY5016): FDA 2015

- large RCTs (AMETHYST-DN, OPAL-HK, PEARL-HF)

<table>
<thead>
<tr>
<th>TRIAL</th>
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<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEARL-HF</td>
<td>DB, PC</td>
<td>105</td>
<td>CHF; K 4.3-5.1 starting aldo ant</td>
<td>15 g bid vs placebo X 4 weeks</td>
<td>( \Delta K ) from baseline</td>
<td>Mean 4.69 PAT: -0.22 Pla: +0.23</td>
<td></td>
</tr>
<tr>
<td>AMETHYST-DN</td>
<td>Open, dose finding</td>
<td>306</td>
<td>DM, CKD, K &gt;5 + ACE or ARB or both</td>
<td>4.2, 8.4 or 12.6 bid for K 5.1-5.5; 8.4, 12.6, 16.8 for K 5.6-5.9</td>
<td>( \Delta K ) from baseline</td>
<td>Mild: range -0.35 to 0.55 Mod: range -0.87 to -0.92</td>
<td>Diuretic use not reported</td>
</tr>
<tr>
<td>OPAL-HK</td>
<td>Blind single arm initial phase followed by randomized single blind, placebo controlled withdrawal phase</td>
<td>243/107</td>
<td>Initial 4 week: CKD 3/4 on RAAS K 5.1-6.4 Randomized 8 week withdrawal: patients with baseline K ( \geq ) 5.5 at initial and 3.8-5 at end of initial</td>
<td>Initial: pat 4.2/8.4 bid X 4 weeks Randomized: continue pat or switch to placebo Randomized: between group diff in median ( \Delta K ) over first 4 weeks or first visit K &lt;3.8 to &gt;5.4</td>
<td>Initial: ( \Delta K ) from baseline Randomized: between group</td>
<td>Initial: -1.01 Randomized: Pat: 0 Placebo: +0.72; Pat: 43% had recurrent HyperK; 94% continued RAAS Placebo: 91%; 44% continued RAAS</td>
<td>Total: Thiazide 29% loop: 32% Randomized phase: Thiazide: pat: 29% vs placebo: 21% Loop: Pat:29% vs placebo: 38%</td>
</tr>
</tbody>
</table>
Patiromer: OPAL-HK

Figure 1. Serum Potassium Levels over Time during the Initial Treatment Phase.
Values are the observed mean values as measured in a central laboratory. During the 4-week initial treatment phase, all patients received treatment with patiromer; patients with a potassium level of 5.1 to less than 5.5 mmol per liter (mild hyperkalemia) received 4.2 g of patiromer twice daily, and those with a potassium level of 5.5 to less than 6.5 mmol per liter (moderate-to-severe hyperkalemia) received 8.4 g of patiromer twice daily. I bars indicate standard errors. Data points are staggered to make them more legible.

Weir et al, NEJM, 372(3)
Patiromer

• Dose dependent reduction in K
• Mean K reduction higher in those with higher baseline K
• Onset: 7-48 hours; duration 12-24 hours
• No sodium load; binds magnesium
• Caucasian populations; low K diet; relatively short duration (52 week)
Patiromer: Safety

- Adverse events (FDA): 734 pts total; 534 > 4 weeks, 219 > 6 mths, 149 > 1 year
- Constipation: 7.2%, hypoMg: 5.3%, diarrhea 4.8%, hypoK 1.5%; no drug-related SAE

Table 34: Summary of Possible Dose related Treatment-Emergent Adverse Events in Study 205 (Safety Population)

<table>
<thead>
<tr>
<th>Event</th>
<th>8.4 g/day N=74</th>
<th>16.8 g/day N=99</th>
<th>25.2 g/day N=101</th>
<th>33.6 g/day N=30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects reporting at least 1TEAE</td>
<td>47 (63.5)</td>
<td>69 (69.7)</td>
<td>70 (69.3)</td>
<td>25 (83.3)</td>
</tr>
<tr>
<td>Constipation</td>
<td>4 (5.4)</td>
<td>5 (5.1)</td>
<td>5 (5.0)</td>
<td>5 (16.7)</td>
</tr>
<tr>
<td>Hypomagnesaemia</td>
<td>4 (5.4)</td>
<td>7 (7.1)</td>
<td>10 (9.9)</td>
<td>5 (16.7)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>2 (2.7)</td>
<td>2 (2.0)</td>
<td>0 (0.0)</td>
<td>3 (10.0)</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>5 (6.8)</td>
<td>9 (9.1)</td>
<td>7 (6.9)</td>
<td>7 (23.3)</td>
</tr>
</tbody>
</table>

(Reviewer table based on the CSR 205 report)
# ZS-9: FDA 2018

- One phase 2 and two phase 3 studies

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>DESIGN</th>
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<th>Pop</th>
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</thead>
<tbody>
<tr>
<td>Anker et al</td>
<td>DB, PC</td>
<td>90</td>
<td>CKD 3; K 5-6</td>
<td>ZS 9 0.3, 3, 10 po tid vs placebo for 48 hours</td>
<td>∆K from baseline</td>
<td>Mean ZS-9: -0.11 to -0.92 Pla: +0.12 to -0.26</td>
</tr>
<tr>
<td>Packham et al</td>
<td>DB, PC, 2 phases</td>
<td>754/543</td>
<td>Initial: outpts with Hyper K (5-6.5) Maintenance: K 3.5-4.9 after 48 hrs from initial phase 60% CKD, 64% RAAS; 40% CHF</td>
<td>Initial: ZS9 varying doses vs placebo Main: dose from initial od vs placebo for 12 days</td>
<td>Initial: ∆K 48 hr from baseline Main: mean K vs placebo over 12 days</td>
<td>Initial: -0.16% to -0.30% per hour vs -0.09% placebo Main: +0.09 to 0.14% per hour vs 0.47 to 1.04% placebo</td>
</tr>
<tr>
<td>HARMONIZE</td>
<td>DB PC</td>
<td>258/237</td>
<td>Initial: outpts with Hyper K &gt;5.1 open label Maintenance: K 3.5-5 after 48 hrs from initial phase 70% CKD, 70% RAAS; 35% CHF</td>
<td>Initial: ZS9 10 tid X 48 hrs Randomized: ZS9 5 to 15 vs placebo for 28 days</td>
<td>Initial: ∆K 48 hr from baseline Main: mean K vs placebo over 29 days</td>
<td>Initial: mean -1.1 (0.3% per hour) Main: mean K 4.8, 4.5, 4.4 for ZS9 vs 5.1 for placebo</td>
</tr>
</tbody>
</table>
ZS-9

- Dose dependent reduction in K
- Mean K reduction higher in those with higher baseline K
- More predictable onset of action; potentially effective in acute hyperK
- Traps ammonium ion in GI tract (improves acidosis)
- 12 month trial results to be published

FDA Approval:
Adverse events (chronic): edema 13.7%, HTN 11%, UTI 7.9%, hypoK 10%
Edema more common in CKD, CHF, CCBs
Theme 1: No clear standard of care

- What are the practice patterns of chronic hyperK management by jurisdictions?
Theme 2: Prevention/Treatment intermixing

- Treatment of non-emergent hyperkalemia: shorter duration; higher intensity; rapid follow up
- Prevention: chronic, long term use
Theme 3: Literature-practice mismatch

Q: Preferred strategy for treatment of chronic hyperkalemia; Twitter poll: N = 218

- Diuretics
- Dose reduction ACEI/ARB
- SPS
- Patiromer or ZS 9

72%!
Theme 4: there are PERSISTENT concerns about SPS

Q: Are you concerned about using SPS orally for hyperK due to adverse GI events; Twitter poll: N = 51

- no (with no sorbitol): 85%
- minor concerns
- major concerns
- very! Never use it

Q: A drug with an AE (hospitalization); alternatives available with a better safety profile; what NNH would stop you from prescribing? Twitter poll: N = 15

- NNH 14
- NNH 140
- NNH 1400
- none; give alternative: 80%
Theme 5: Newer binders studies: questions remain

- All placebo! Need active comparator studies of diuretics or dose reductions or each other; no comparative effectiveness studies pending (clinicaltrial.gov)
- Need to separate treatment from prevention
- Population-based observational studies for safety data (for SPS our study had over 27,000 exposures!)
Theme 6: no idea what to do for dialysis

Newer binder studies in the works
Thank you

- KDIGO organizing committee
- Research Team: Ariana Noel, Sarah E Bota, William Petrcich, Ziv Harel, Navdeep Tangri, Paul Komenda, Amit X Garg, Emily Rhodes
- Institute for Clinical Evaluative Sciences
- Ottawa Hospital Research Institute
- Jindal Research Chair for the Prevention of Kidney Disease