What’s new on Hyperkalemia

8:30-9:00
September 13, 2019

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Professor, Emergency Medicine
Associate Chair and Research Director
Baylor College of Medicine
Rates of Hyperkalemia

Annual ED visits for Hyperkalemia¹

- 847,079 with hyperkalemia as a diagnosis
- 70,394 with hyperkalemia as primary

64% of these patients belong to Medicare

Nearly 50% of ED visits for primary hyperkalemia result in hospitalization¹

About 2 in 10 patients have hyperkalemia (K⁺ ≥5 mEq/L) upon initiation of critical care²

*Data taken from the Healthcare Cost and Utilization Project’s nationwide ED sample, 2013. Hyperkalemia diagnoses are based on ICD-9 code 276.7.¹ †Retrospective observational study of 39,705 patients who received critical care between 1997 and 2007 at 1 of 2 tertiary care hospitals in Boston. Serum potassium was measured at initiation of critical care.²

How does this happen?

Marker of disease
• Overdose
  – Digoxin, Fluorine
• Metabolic diseases
  – Addison’s
• Trauma/Burns
  – Cubozoan envenomations
• Screw ups
  – Transfusion reaction
• Weird stuff
  – Toad eating

We do it to you
• ACEI, ARBs
• MRAs
• NSAIDs
• Antibiotics (bactrim, PCN)
• Heparin
• Salt substitutes
• K\(^+\) sparing diuretics
• β-blockers
• Calcineurin inhibitors
• Azole antifungals
Toad Soup Cluster

- Family ate toad soup
  - 15 m old died, bradycardia
  - 20 m old, K=7.3, AVB, shock
    - Tx: atropine, lidocaine, cardioversion, TVP
  - 16 y old; K=6.3 mEq/L, bradycardia.
  - 3 adults N/V/D oral mucosa numbness

- K level has prognostic implications in toad intoxication

Human & Exp Tox (1998) 17, 343 ± 346
## Comorbidities and Med Use in Hospitalized Pts w K > 5.1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>AKI</td>
<td>62%</td>
</tr>
<tr>
<td>CKD</td>
<td>51.8%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>42%</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
<td>36.6%</td>
</tr>
<tr>
<td>ACE/ARB use</td>
<td>32%</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>23%</td>
</tr>
<tr>
<td>Eplerenone/spironolactone use</td>
<td>17%</td>
</tr>
</tbody>
</table>

Longer duration of hyperK = mortality  
(OR 1.06, 95% CI 1.02-1.09; \(P<0.001\))  

All Hyperkalemia goes to the ER
100,260 visits in 2014
K ordered in 48,827 (49%)
1,738 (3.6%) hemolyzed

5.5% low (<3.5)
90.9% normal (3.5 - 5.0)
3.6% elevated (>5.0)
Hector Martinez

• 1:20 am, 36 yo hispanic male presents to ED with N/V, general malaise
• History of ESRD, last dialysis 6 days ago
• HR 87, O₂ sat 94%
• Neck: No jvd
• Lungs: CTA
• Heart: No rub, No S3
• Ext: trace edema
1:24 am

POC K⁺ = 6.6
Options @ 2:50 am

**Definitive**
- Dialysis

**Buy time**
- Calcium
- Alkalinze
- Glucose / Insulin
- Beta Adrenergics
- Loop diuretics
- Binding resins
Calcium

- Acts quickly, can be lifesaving
- 1st-line tx if ECG sig abnl
  - Not indicated if only peaked T waves.
- Increases threshold potential
  - Tbhldd and resting membrane potential is restored in hi K
- 1 amp of CaCl₂ 3x > Ca ++
  - Gluconate
- Onset < 5 min, lasts 30-60 min.
- Titrate to ECG changes during administration
- Repeat if ECG doesn’t normalize within 3-5 min.

Buys you 30 minutes
Alkalization

- Increases urine and blood pH, causes temporary $K^+$ shift from ECF to ICF
- Onset minutes, lasts 15-30 min.
- Likely to work only if underlying acidosis present
- Enhances the effect of insulin in acidotic pts
- Use 8.4% solution in adults and children, 4.2% solution in infants.
Glucose and Insulin

- Insulin given IV with glucose
  - increases glucose transfer into cell
  - brings $K^+$ with it.
- Temporarily shifts $K^+$ into cells
  - onset within 30 min of administration
  - monitor blood glucose levels closely
  - buys you 2 hours (maybe more)
Beta_2 Adrenergic Agonists

- Promotes cellular reuptake of K^+ possibly by cyclic GMP receptor cascade.
- Also increases insulin levels
- May help shift K^+ into ICF
- Lower K^+ by 0.5 - 1.5 mEq/L.
- Can be useful in ESRD when vol load is a concern
- Onset 30 min; duration 2 - 3 h

Buys you 2 hours
Loop Diuretics

- Causes renal K loss

Buys nothing

Doesn’t Work in Renal Failure
Tx of HK in the ED: What is the Standard?

Insights from the REVEAL-ED Trial questionnaire
Q7: Please indicate at what potassium levels you treat hyperkalemia acutely with the following? (Insulin, Albuterol, Bicarbonate, Diuretic, Kayexalate)

<table>
<thead>
<tr>
<th></th>
<th>Insulin</th>
<th>Albuterol</th>
<th>Bicarbonate</th>
<th>Diuretic</th>
<th>Kayexalate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>K^+ Level (mEq/L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5.5</td>
<td>5</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>5.5-&lt;6</td>
<td>21</td>
<td>18</td>
<td>18</td>
<td>53</td>
<td>37</td>
</tr>
<tr>
<td>6-&lt;6.5</td>
<td>74</td>
<td>71</td>
<td>76</td>
<td>35</td>
<td>47</td>
</tr>
<tr>
<td>≥6.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

(n=19) (n=17) (n=17) (n=17) (n=19)
Most PIs opt for 6 mEq/L for Dialysis

Q.6 - Threshold for Dialysis
Percentage of Respondents

<table>
<thead>
<tr>
<th>K⁺ Level (mEq/L)</th>
<th>Without ESRD (n=9)</th>
<th>With ESRD (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>44</td>
<td>14</td>
</tr>
<tr>
<td>6.5</td>
<td>44</td>
<td>14</td>
</tr>
<tr>
<td>7</td>
<td>11</td>
<td>21</td>
</tr>
</tbody>
</table>
K Measurement Varies

Q8: How often do you measure potassium levels when patients are treated for hyperkalemia in the ER?

Percentage of Respondents (n=18)

KEY OBSERVATIONS

- 94% measure K q 1-4 h
- Only 61% measure K more often than q 2 h
- Only 17% measure q 1 h
- Only one PI (6%) measures K less often than q 4 h
REVEAL Study Design

**Screening:**
- SOC potassium
- Subject’s chief complaints upon arrival at ED
- Assess possible cause of HK
- NYHA assessment if history of HF

**Initial Intervention/Treatment**
- Blood draws to measure potassium levels
- Concomitant medications assessment

SOC = standard of care.
Treatments Over 4 Hours

![Bar chart showing the percentage of patients receiving different treatments over 4 hours.](chart.png)
Treatments

4-Hour Time Point

144 different treatments

Beta2: beta2 agonists, Insulin: insulin/glucose, SPS: sodium polystyrene sulfonate.
K+ Levels From Start of Treatment

Evaluable Population - Excluding Patients Who Received Dialysis

Median (IQR) Potassium Levels (mEq/L) vs Time (Hours)

<table>
<thead>
<tr>
<th>Time (Hours)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>120</td>
</tr>
<tr>
<td>1</td>
<td>53</td>
</tr>
<tr>
<td>2</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>120</td>
</tr>
</tbody>
</table>

NO DIALYSIS
K+ Levels From Start of Treatment

Evaluable Population - Patients Who Received Dialysis

Median (IQR) Potassium Levels (mEq/L) vs Time (Hours)

DIALYSIS

<table>
<thead>
<tr>
<th>Time (Hours)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>41</td>
</tr>
<tr>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>41</td>
</tr>
</tbody>
</table>
K+ Levels From Start of Treatment

Evaluable Population - Excluding Patients Who Received Dialysis

<table>
<thead>
<tr>
<th>Time (Hours)</th>
<th>Monotherapy</th>
<th>2 Therapies</th>
<th>3 Therapies</th>
<th>4 Therapies</th>
<th>≥5 Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6.5</td>
<td>6.0</td>
<td>6.0</td>
<td>6.0</td>
<td>6.0</td>
</tr>
<tr>
<td>1</td>
<td>6.0</td>
<td>5.5</td>
<td>5.5</td>
<td>5.5</td>
<td>5.5</td>
</tr>
<tr>
<td>2</td>
<td>5.5</td>
<td>5.0</td>
<td>5.0</td>
<td>5.0</td>
<td>5.0</td>
</tr>
<tr>
<td>3</td>
<td>5.0</td>
<td>4.5</td>
<td>4.5</td>
<td>4.5</td>
<td>4.5</td>
</tr>
<tr>
<td>4</td>
<td>4.5</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
<td>4.0</td>
</tr>
</tbody>
</table>

n = 7

Median (IQR) Potassium Levels (mEq/L)

- Monotherapy
- 2 Therapies
- 3 Therapies
- 4 Therapies
- ≥5 Therapies
## Recordable Outcomes*

### Occurring in ≥5 Patients

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Baseline Potassium (mEq/L)</th>
<th>All Patients (n = 199)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;6.0 (n = 64)</td>
<td>≥6.0 to 6.5 (n = 63)</td>
</tr>
<tr>
<td>GI disorders</td>
<td>6 (9)</td>
<td>9 (14)</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>5 (8)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>–</td>
<td>3 (5)</td>
</tr>
<tr>
<td>GI bleed</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Cholecystitis</td>
<td>–</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Hypoglycemia‡</td>
<td>1 (2)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>4 (6)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Cardiac event</td>
<td>1 (2)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>HF</td>
<td>1 (2)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Death</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>–</td>
<td>1 (2)</td>
</tr>
<tr>
<td>NSTEMI, HF</td>
<td>–</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Hemodynamic instability</td>
<td>1 (2)</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

*Collected through discharge from ED or, if admitted to another unit, up to 7 days after admission to that unit or discharge from that unit if earlier.

†4 patients did not have baseline potassium values.

‡Hypoglycemia caused by insulin/glucose in 9 patients (7% of insulin/glucose-treated patients).
### ECG Changes Related to HK*

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Baseline Potassium (mEq/L)</th>
<th>All Patients (n = 199)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;6.0 (n = 64)</td>
<td>42 (21)</td>
</tr>
<tr>
<td></td>
<td>≥6.0 - 6.5 (n = 63)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;6.5 - 7.0 (n = 43)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;7.0 (n = 29)</td>
<td></td>
</tr>
<tr>
<td>Peaked T</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 (9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16 (25)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 (16)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>13 (45)</td>
<td></td>
</tr>
<tr>
<td>Prolonged QRS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 (13)</td>
<td>24 (12)</td>
</tr>
<tr>
<td></td>
<td>4 (6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 (12)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 (24)</td>
<td></td>
</tr>
<tr>
<td>Peaked T and/or Prolonged QRS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11 (17)</td>
<td>53 (27)</td>
</tr>
<tr>
<td></td>
<td>17 (27)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10 (23)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15 (52)</td>
<td></td>
</tr>
</tbody>
</table>

- New ECG changes were reported in 8 patients
- Arrhythmias were reported in 3 patients

*Considered definitely, probably or possible related to hyperkalemia by the investigator.
†4 patients did not have baseline potassium values.
Old and New Options: Ion Exchange Resin

- Sodium polystyrene (Kayexalate)
- Patiromer
- ZS-9
Binding Resins

- Onset 2-12 hours
- Causes diarrhea, usually refused by pt
FDA Warns of Treating Patients with Organic Polymers Due to Colonic Necrosis

FDA
U.S. Food and Drug Administration
Protecting and Promoting Your Health

Kayexalate (sodium polystyrene sulfonate) powder

Detailed View: Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER)

January 2011
Summary View

WARNINGS
Colonic Necrosis
- Cases of intestinal necrosis, which may be fatal, and other serious gastrointestinal adverse events (bleeding, ischemic colitis, perforation) have been reported in association with Kayexalate use.
- Do not use in patients who do not have normal bowel function. This includes postoperative patients who have not had a bowel movement post surgery.
- Do not use in patients who are at risk for developing constipation or impaction (including those with history of impaction, chronic constipation, inflammatory bowel disease, ischemic colitis, vascular intestinal atherosclerosis, previous bowel resection, or bowel obstruction).
- Discontinue use in patients who develop constipation. Do not administer repeated doses in patients who have

PRECAUTIONS
Sorbitol
- Concomitant use of Sorbitol with Kayexalate has been implicated in cases of colonic intestinal necrosis, which may be fatal.

Pediatric Use
- the word “Colonic” was replaced with “Intestinal.”

ADVERSE REACTIONS
- “hypomagnesemia” was added after the words “hypokalemia, hypocalcemia.”
- “colonic” was replaced with the word “intestinal” [seventh sentence of the first paragraph]
- “Ischemic colitis” was added in front of the words, “gastrointestinal tract.” [the third bullet]
- text deleted: “Magnesium-containing laxatives or sorbitol should not be used (See PRECAUTIONS, Drug Interaction)”

Source: FDA Website
Ion-Exchange Resins for the Treatment of Hyperkalemia: Are They Safe and Effective?

We can find no convincing evidence that SPS increases fecal potassium losses in experimental animals or humans and no evidence that adding sorbitol to the resin increases its effectiveness as a treatment for hyperkalemia. There is growing concern, however, that suspensions of SPS in sorbitol can be harmful. It would be wise to exhaust other alternatives for managing hyperkalemia before turning to these largely unproven and potentially harmful therapies.

Patiromer

- Oral suspension
- Non-absorbed polymer
- Binds K thru the gi tract
- Increases fecal excretion
- Smooth, spherical, beads
- ~100μm diameter
- Do not swell appreciably in liquids
Patiromer: A Nonabsorbed Metal-Free Polymer

Patiromer’s Physical and Chemical Properties Optimize MOA

- Ca (instead of Na) is exchanged for K⁺
- Site of action is the lumen of the colon, where [K⁺] is the highest and the residence time of the polymer is the longest; does not rely on preventing absorption of dietary K⁺ for effect
- Not absorbed and not metabolized or changed by GI passage; favorable flow properties

Study Design

**Part A: Treatment Phase (Single-Blind)**
(4 Weeks)

- **Mild HK**
  - Screening serum K\(^+\) 5.1 to <5.5 mEq/L; 4.2 g BID starting dose (n=92)

- **Moderate to Severe HK**
  - Screening serum K\(^+\) 5.5 to <6.5 mEq/L; 8.4 g BID starting dose (n=151)

**Part B: Randomized Withdrawal Phase (Single-Blind)**
(8 Weeks)

- At week 4
  - K\(^+\) 3.8 to <5.1
  - Still on patiromer
  - Still on RAASi (n=107)

- Randomization

- Patiromer, continued RAASi (n=55)
- Placebo, continued RAASi (n=52)

**Subjects with CKD* on RAASi (N=243)**

* eGFR 15-60 ml/min/m\(^2\)

Randomization.

CKD, chronic kidney disease; RAASi, renin-angiotensin-aldosterone system inhibitors.
Effect of Patiromer on Serum K⁺ in Patients With and Without Heart Failure During the Treatment Phase (Part A)

**Mean (±SE) Serum K⁺ Change from Baseline (mEq/L)**

- **Heart Failure**
  - Day 3: -0.5±0.05
  - Week 1: -0.8±0.05
  - Week 2: -0.9±0.05
  - Week 3: -1.1±0.05
  - Week 4: -1.1±0.05

- **No Heart Failure**
  - Day 3: -0.5±0.04
  - Week 1: -0.7±0.04
  - Week 2: -0.9±0.04
  - Week 3: -1.0±0.04
  - Week 4: -1.0±0.04

Means were adjusted for baseline serum K⁺ and the presence of T2DM and HF.

**Treatment Phase Primary Endpoint:**
Mean Change from Baseline to Week 4

- **Heart Failure**
  - Mean Baseline: 5.6 mEq/L
  - Mean Week 4: 4.5 mEq/L
  - Change: -1.1±0.05 mEq/L
  - (95% CI, -1.16, -1.05)
  - p<0.001

- **No Heart Failure**
  - Mean Baseline: 5.5 mEq/L
  - Mean Week 4: 4.5 mEq/L
  - Change: -1.0±0.04 mEq/L
  - (95% CI, -1.06, -0.90)
  - p<0.001

**Secondary Endpoint:**
76% and 75% of patients with and without HF, respectively, had serum K⁺ 3.8 to < 5.1 mEq/L at Week 4.

p=0.22 for interaction
Or earlier time point if patient first had serum $K^+ < 3.8$ mEq/L or $\geq 5.5$ mEq/L.

†$p<0.001$ for between-group difference in mean ranks of change.

p=0.50 for interaction between HF vs no HF
During the Treatment Phase (Part A): Patiromer Safety Summary

<table>
<thead>
<tr>
<th>Treatment Phase</th>
<th>Heart Failure N=102 n (%)</th>
<th>No Heart Failure N=141 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients reporting ≥ 1 adverse event</td>
<td>42 (41%)</td>
<td>72 (51%)</td>
</tr>
<tr>
<td>Serious</td>
<td>2 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Leading to patiromer discontinuation</td>
<td>7 (7%)</td>
<td>8 (6%)</td>
</tr>
<tr>
<td>Most common individual AE*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild-to-moderate constipation</td>
<td>11 (11%)</td>
<td>15 (11%)</td>
</tr>
<tr>
<td>Electrolytes of interest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia (serum K⁺ &lt;3.5 mg/dL)</td>
<td>3 (3%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Serum magnesium &lt;1.2 mg/dL</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hyponatremia reported as adverse event</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Hypercalcemia reported as adverse event</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*All other individual adverse events occurred in ≤4% patients with HF and ≤5% of patients without HF.
Unpublished
ZS-9 Selective Potassium Trap

**ZS-9 PROPERTIES**

- Unique microporous zirconium silicate compound
- Designed to be selective for K\(^+\) trapping
- Insoluble and highly stable
- Non-systemically absorbed
- Builds on long history of Zr use in dialysis and other biomedical applications

ZS-9 Crystal Structure

Average Width of Micropore Opening 3Å
Long History of Safe Zirconium Use in Man

Most comprehensive study of Zr was conducted by Schroeder and Balassa,¹ Lee recently reviewed current biomedical uses²

- Daily Zr intake is estimated to be 1-9 mg per day
- Experimental toxicity studies demonstrate that Zr is inert and low toxicity making it well suited for biomedical applications

Zirconium containing compounds safely used in many biomedical applications

- Nephrology (hemodialysis, peritoneal dialysis, hemofiltration)
- Dental implants and other restorative practices
- Middle ear ossicular chain reconstruction

Safely used in Patients with CKD

- 2,000,000 dialysis treatments with REDY and Sorb columns since 1970³
- Fresenius’s DIALISORB is under development as a dialysate filter⁴
- Fresenius developing Zr based Wearable Artificial Kidney

# Zirconium Containing Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>85g Antiperspirant Stick(^1)</td>
<td>2295 mg</td>
</tr>
<tr>
<td>Soil(^2)</td>
<td>300 mg/L</td>
</tr>
<tr>
<td>Human Body Content(^4)</td>
<td>300 mg</td>
</tr>
<tr>
<td>Daily Food Content(^3)</td>
<td>3.65 mg</td>
</tr>
<tr>
<td>Zr From 4Hr Sorbent Hemodialysis(^4)</td>
<td>0.758 mg</td>
</tr>
<tr>
<td>Daily Drinking Water Content(^3)</td>
<td>0.65 mg</td>
</tr>
<tr>
<td>Absorption from Antiperspirant(^1,2)</td>
<td>0.0046 mg/app.</td>
</tr>
<tr>
<td>Sea Water(^3)</td>
<td>0.004 mg/L</td>
</tr>
<tr>
<td>Soluble from 10g ZS-9(^5)</td>
<td>0.00028 mg</td>
</tr>
</tbody>
</table>

---

**SOURCE:**
ZS-9 Pores/Windows Utilize Energetically Favorable Size Selectivity Filter Similar to Physiologic Ion Channels in Cell Membranes

Energy to dehydrate the ion is more than balanced by the energy regained by the interaction with carbonyl oxygens.

Because Ca$^{+2}$ is too small to interact with the oxygens, entering the pore/window is energetically unfavorable.
**ZS-9: In Vitro Ion Exchange Capacity and Selectivity**

*Selectivity Ratio* = \([K^+] / [Ca^{2+}] + [Mg^{2+}]\)

**Exchange capacity of Ca\(^{2+}\) and Mg\(^{2+}\) was below the 0.05 detection limit; therefore, 0.05 assumed for calculation purposes.

**KEY OBSERVATIONS**

- 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\(^+\)
ZS 9 Drug Interactions

- The only clinically significant interaction described to date is Lithium.

- Decreases the K exchange capacity of ZS-9 by **12%** (ZS Pharma, data on file).

  — attributed to the similarity in size of the lithium ion to that of K.
Study ZS-004: Study Design

48-Hour
Open Label Phase

- OPEN-LABEL
  - ZS-9 10g TID (n=258)

Patients who achieve normokalemia (K⁺ 3.5-5.0 mEq/L) proceed to Randomized Phase

28 Day
Randomized Phase

- DOUBLE-BLIND, RANDOMIZED
  - ZS-9 vs Placebo (n=237)
    - 7: Placebo QD
    - ... 4: ZS-9 5g QD
    - ... 4: ZS-9 10g QD
    - ... 4: ZS-9 15g QD
Study ZS-004: ZS-9 (10g) Significantly Reduced Serum K⁺ Levels Over 48 Hrs

KEY OBSERVATIONS

- Mean starting K⁺ of 5.55 mEq/L
- 0.2, 0.4, & 0.5 mEq/L potassium decline at 1, 2, & 4 hours respectively (p<0.001)
- Median time to K⁺ normalization 2.2 hours
- 84% of patients normalized by 24 hrs
- 98% of patients normalized by 48 hrs

*P value <0.001
ZS-9 Maintained Mean Serum K⁺ Within Normal Levels Across the Maintenance Phase (Days 8-29)

* Two-sample t-test p-value <0.05

ZS Doses:
- Placebo (n=82)
- 5g ZS-9 (n=45)
- 10g ZS-9 (n=50)
- 15g ZS-9 (n=54)

Primary Endpoint

Mean Serum Potassium (mEq/L)

Time (Day)

SOURCE: 14.2.2.7.1
### Acute Phase AE Rates Similar Across Studies ZS-003 and ZS-004

<table>
<thead>
<tr>
<th>Acute Phase</th>
<th>All AEs</th>
<th>GI AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo (ZS-003)</strong> (n=158)</td>
<td>10.8</td>
<td>5.1</td>
</tr>
<tr>
<td><strong>ZS-9 10g (ZS-003)</strong> (n=143)</td>
<td>11.9</td>
<td>3.5</td>
</tr>
<tr>
<td><strong>ZS-9 10g (ZS-004)</strong> (n=258)</td>
<td>7.8</td>
<td>3.9</td>
</tr>
</tbody>
</table>

**All AEs and GI AEs (Acute Phase) – Placebo vs ZS-9 10g TID**

Percent

**SOURCE:** 14.3.2.2.1; t_a016ag_01

Biostats Review and QC pending
ZS9 for Acute K$^+$ Lowering in Patients With Severe Hyperkalemia

• Two phase 3 randomized trials
  – N >1,000 pts showed ZS-9 effectively lowered K$^+$ in a broad cross-section of hyperkalemic patients.$^{1,2}$

  1 Packham DK. NEJM 2014 Nov 21 [ePub ahead of print]
  2 Kosiborod M. JAMA 2014; 312: 2223-2233

• Subset with K$^+$ of $\geq$6.0 mmol/L
  – N = 45, treated with 10g ZS-9

• Purpose: define acute changes in K$^+$ within 4 hours after a 10g dose of ZS-9

Time vs Potassium

Δ $K^+$ after 10g ZS9

• By 4 hours
  – 80% of patients had $K^+ < 6.0$ mmol/L
  – 52% had $K^+ \leq 5.5$ mmol/L

• ZS-9 was well tolerated with no serious adverse events or cases of hypokalemia ($K^+ < 3.5$ mmol/L) during the initial 48 hours.

Unpublished
Summary

• Patiromer and ZS9 are effective at lowering K in pts with RAASi indications who would otherwise be limited from taking guideline recommended doses.

• Both have few side effects
  – Patiromer black box for binding
  – ZS9 ? Edema

• ZS9 with potentially acute usage
IN ANY CASE: Treat and cure
1) The cause of hyperkalemia
   - associated disorders (e.g., treatment of shock, correction of hypovolemia or heart failure, or treat the cause of AKI)
2) K+-related Changes on EKG?
   - Cardiac monitoring
   - Ca gluconate or chloride i.v.

Consider pseudohyperkalemia

If acute hypovolemia and metabolic acidosis, consider sodium bicarbonate i.v.

Severe Acute Kidney Injury?

Decrease of K+ serum level

- ReConsider treatment leading to hyperkalemia
- Discontinue oral and parenteral potassium supplements

Consider dialysis

Consider semi-urgent Dialysis initiation

Rossignol P. Pharmacological Research 113 (2016) 585–591