EVIDENCE FOR MANAGEMENT OF HYPOKALEMIA IN THE ED, CKD AND DIALYSIS PATIENTS

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DISCLOSURES

• Editor, Kidney Self Assessment Program, American Society of Nephrology
AGENDA
1. Consequences of hypokalemia
2. Screening for hypokalemia
3. Treatment
   What interventions are used to treat hypokalemia
   - IV, oral supplements, K sparing diuretics
   Data on treatment effectiveness in raising potassium
   - preventing clinically-important hypokalemia-related outcomes
   Potential harms of treatment
   - risk of hyperkalemia
   - Clinically important adverse effects of therapy.
   After hypokalemia event: monitoring, retesting
4. Risks and treatment of hypokalemia in ESRD
1. CONSEQUENCES OF HYPOKALEMIA

- **Muscle--**
  - Skeletal muscle weakness (can be insidious), Myopathy, and rhabdomyolysis
  - Smooth muscle dysfunction and a paralytic ileus
  - Cardiac manifestations: excitable (potential increased risk of arrhythmia with MI or anaesthesia)

- **Renal manifestations**
  - concentrating defect (decreased medullary gradient and resistance to ADH)
  - kaliopenic tubulopathy (tubular atrophy, interstitial fibrosis, macrophage infiltration)

- **Glucose intolerance**
Cardiac myocytes become more excitable

Muscle becomes less excitable

ST depression
T wave flattening
U waves

Descending ST
delayed repolarization and more excitable
(may be exacerbated by glycosides)
(? Increased risk of arrhythmia with anaesthesia?)

Nerves/muscle

Adapted from Lerma et al. Current Diagnosis and Treatment 2nd Ed
Over 3 years, 11% of 43,800 patients had $K^+ < 3.5$
53 of these (1%) had severe hypokalemia $< 2.6$
69% of these had ECG manifestations of hypokalemia
Risk of VT/VF with hypokalemia may be greatest in the setting of acute MI

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of Patients</th>
<th>Association</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hulting(^49)</td>
<td>1,315</td>
<td>Yes</td>
<td>Potassium &lt;3.9 mEq/L associated with 5-fold increase in VT(^*)</td>
</tr>
<tr>
<td>Solomon and Cole(^50)</td>
<td>151</td>
<td>Yes</td>
<td>VT/VF in 48% of patients with potassium &lt;3.5 mEq/L vs 21% with potassium &gt;3.5 mEq/L</td>
</tr>
<tr>
<td>Nordrehaug(^51)</td>
<td>1,035</td>
<td>Yes</td>
<td>VF in 16% of patients with potassium &lt;3.5 mEq/L vs 7% with potassium &gt;3.5 mEq/L†</td>
</tr>
<tr>
<td>Nordrehaug et al(^52)</td>
<td>60</td>
<td>Yes</td>
<td>Probability of VT 0.68 with potassium &lt;3.5 mEq/L vs 0.10-0.22 with potassium &gt;4.0 mEq/L</td>
</tr>
<tr>
<td>Nordrehaug and Von der Lippe(^53)</td>
<td>1,074</td>
<td>Yes</td>
<td>VF in 17.2% of patients with potassium &lt;3.5 mEq/L vs 7.5% with potassium &gt;3.5 mEq/L†</td>
</tr>
<tr>
<td>Dyckner et al(^54)</td>
<td>676</td>
<td>Yes</td>
<td>VT/VF in 40% of patients with potassium &lt;4.3 mEq/L vs 27% with potassium &gt;4.3 mEq/L†</td>
</tr>
<tr>
<td>Johansson et al(^55)</td>
<td>5,877</td>
<td>Yes</td>
<td>Incidence of VF increased by 2.0- to 2.5-fold when potassium &lt;3.5 mEq/L†</td>
</tr>
</tbody>
</table>

\(^*P < 0.05.\)  
\(^†P < 0.01.\)  
\(^‡P < 0.001.\)
Preoperative potassium and perioperative outcomes in cardiac surgery patients

Risk of CPR

Risk of Death

24 centers and 2402 patients

Wahr JA JAMA 1999
Risk of ventricular arrhythmia by Holter according to potassium in thiazide treated men

266 HTN men on 6 regimens:
- 50 HCTZ (K⁺ 3.78)
- 50 HCTZ + 40 KCl
- 50 HCTZ + KCl + 400 mg Mg
- 50 HCTZ + 100 triamterine
- 50 chlorthalidone (K⁺ 3.47)

Most did not develop hypokalemia or arrhythmia

Siegal D et al JAMA 1992
Thiazide induced hypokalemia is associated with glucose intolerance

59 clinical trials with 83 trial arms

Zillich A Hypertension 2006
2. Common recommendations in the literature regarding screening for \( K^+ \) (and creatinine/eGFR)

- In patients with history of losses, symptoms of hypokalemia, medications or disorders which cause alterations in potassium
- Preoperative testing-- in patients at risk for AKI and/or systemic illness
- With use of thiazide or loop diuretics:
  - Baseline
  - 1-2 weeks after dose increase or relevant dose addition in low risk patients
  - 5-7 days after dose increase or relevant dose addition in high risk patients
  - During intercurrent illness
  - Every 3-6 months in high risk patients
  - Annually in low risk patients
5.2. Diagnostic Tests

**CLASS I**

1. Initial laboratory evaluation of patients presenting with HF should include complete blood count, urinalysis, serum electrolytes (including calcium and magnesium), blood urea nitrogen, serum creatinine, glucose, fasting lipid profile, liver function tests, and thyroid-stimulating hormone. *(Level of Evidence: C)*

2. Serial monitoring, when indicated, should include serum electrolytes and renal function. *(Level of Evidence: C)*

3. A 12-lead electrocardiogram should be performed initially on all patients presenting with HF. *(Level of Evidence: C)*
Recommendations for monitoring in the treatment of patients with heart failure

3. The effect of HF treatment should be monitored with careful measurement of fluid intake and output, vital signs, body weight that is determined at the same time each day, and clinical signs and symptoms of systemic perfusion and congestion. Daily serum electrolytes, urea nitrogen, and creatinine concentrations should be measured during the use of intravenous diuretics or active titration of HF medications. *(Level of Evidence: C)*
Hypokalemia in thiazide use

• Hypokalemia is common but not the rule
  • ALLHAT substudy (19,731 with normal baseline K⁺): 3.5% had hypokalemia (<3.2) on chlorthalidone 12.5 or 25 mg
  • SHEP 4,736 participants on chlorthalidone 12.5 or 25, 7.2% with hypokalemia (<3.5 mmol/L) at 1 year.

• In otherwise healthy individuals, K⁺ depletion is not progressive

• Salt restriction tends to limit K⁺ loss
3. Goals for treatment of hypokalemia

- Identify cause
- Recognize the deficit
  - Deficit calculations
    some examples in the literature: for every 1 mmol/L decrease, 100-200 deficit; for every decrease of 0.3, deficit of 100, if less than 3.0 mmol/L, 200-500 deficit
    \[ K \text{ deficit} = (K_{\text{normal lower limit}} - K_{\text{measured}}) \times \text{kg body weight} \times 0.4 \]
- Address ongoing losses
- Avoid hyperkalemia and toxicity of therapy
- Interval reassessment
- Recognize that treatment of hypokalemia can impact rate of correction in the treatment of hyponatremia
Early literature suggests caution with $K^+$ supplements and wonders whether supplements are needed

- 1839 James Blake injected potassium salt into a dog and it was fatal
- 1881, Feltz and Ritter injected a similar dose slowly over 10 min and there were no adverse effects
- 1942, Keith, Osterburgh and Burchell had normal volunteers ingest massive doses of KCl (here 167 mmol)
Dietary potassium- stay tuned
4. Options for treatment:

Intravenous KCl infusion

• Indications:
  • Unable to tolerate enteral form
  • Severe hypokalemia (<2.5 mmol/)
  • Hypokalemic symptoms or signs
  • ECG changes

• Route of administration (central vs peripheral venous access)
• Limit total potassium in any container
• Rate controlled infusion rather than “push”
Retrospective review of effect KCl infusion

- On average, 1 infusion increased serum K by 0.25 mmol/L

- 1462 infusions over 5 months in ICU

- Infusions of 20 mmol KCl in 100 ml NS over 1 hour

Kruse & Carlson Archives 1990
Intravenous potassium infusion

Average incremental potassium concentration (ΔK) per 20 mmol/L of KCl infusion and per infusion set was 0.25-0.5

<table>
<thead>
<tr>
<th>No. of Consecutive Infusions</th>
<th>No. of Infusion Sets</th>
<th>Mean ΔK, mmol/L</th>
<th>Mean ΔK per Infusion, mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47</td>
<td>0.46</td>
<td>0.46</td>
</tr>
<tr>
<td>2</td>
<td>178</td>
<td>0.50</td>
<td>0.25</td>
</tr>
<tr>
<td>3</td>
<td>170</td>
<td>0.65</td>
<td>0.32</td>
</tr>
<tr>
<td>4</td>
<td>73</td>
<td>0.93</td>
<td>0.46</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>0.99</td>
<td>0.49</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>1.26</td>
<td>0.63</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>0.95</td>
<td>0.47</td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>1.30</td>
<td>0.16</td>
</tr>
</tbody>
</table>
KCI infusion in critically ill patients with hypokalemia

- Prospective study of 40 patients with hypokalemia who received 20 mmol KCl in 100 ml NS over 1 hour either via central or peripheral vein

Kruse J. J Clin Pharm 1994
KCl infusion in critically ill patients with hypokalemia

- Maximum increase in the serum potassium was 0.5 mmol/L and on average, the increase was 0.25 after 1 hour.
Oral supplements have improved-

- Patients were instructed to mix this combination daily and divide into 3 portions:

  Milk
  Cream
  Egg
  Sugar
  Potassium chloride

  1 quart
  ½ cup
  1
  2 teaspoonfuls
  8 teaspoonfuls (30 gm.)

Talbott and Schwab NEJM 1940
Oral supplements of KCl for treatment of hypokalemia

• Oral route whenever possible though $ and pill burden can limit adherence
• Dosage range from 8-100/d and typical dose is 20 mmol/d. Limit to 40 mmol/dose
• Nausea, vomiting, flatulence, abdominal pain and discomfort, diarrhea

Some images of potassium supplements from the PDR
Oral potassium salts

- **Oral KCl-**
  - Liquid-20 or 40mmol/15 mL- often poorly tolerated, unpleasant taste
  - Powder-20 or 25 mmol/packet
  - Slow release –
    - wax matrix –Slo K, Klotrex, KlorCon-- wax matrix associated with GI bleeding
    - microencapsulated formulation (ER) Micro-K 8, 10 mmol/capsule-can also cause gastric ulcers

- **Oral Kphos-useful when hypophosphatemia present**
  - “original” 500 mg tab (3.7 mmmol K+); K-phos neutral (just 1.1 mmol/tab)

- **Oral KHCO₃ (or an organic anion precursor of bicarbonate such as citrate)**
  - Potassium bicarbonate (Klor-Con/EF) 25 mmol tab
  - Potassium citrate 5 mmol, 10 mmol, 15 mmol tabs

some available formulations in US
Pharmacokinetics of two KCl supplements

5 healthy volunteers

<table>
<thead>
<tr>
<th>Time from dosing (h)</th>
<th>Placebo</th>
<th>64 mmol sugar-free syrup Kay-Cee-L</th>
<th>8 tabs X 8 mmol Sugar-coated Wax-based Slow-K</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>15</td>
<td>**</td>
<td>**</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>***</td>
<td>**</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>***</td>
<td>**</td>
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<td>6</td>
<td>10</td>
<td>***</td>
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<td>8</td>
<td>5</td>
<td></td>
<td>**</td>
</tr>
<tr>
<td>12</td>
<td>5</td>
<td></td>
<td>**</td>
</tr>
<tr>
<td>36</td>
<td>5</td>
<td></td>
<td>**</td>
</tr>
</tbody>
</table>

Toner JM Br J Clin Pharmac 1985
K-sparing diuretics

• Blockade epithelial Na⁺ Channel
  • Triamterene-50 mg, 100 mg capsule
  • Amiloride- 5mg tablets

• Mineralocorticoid antagonists
  • Spironolactone-25 mg, 50 mg, 100 mg tablets
    GI intolerance, gynecomastia
  • Eplerone-25 mg, 50 mg tablets
    less GI intolerance
K⁺ Restoration from HCTZ-induced hypokalemia

447 patients treated with 50 mg HCTZ
53% hypokalemia randomized to 3 regimens

- △ 75 mg triamterene
- • 40 mmol KCl
- ○ 20 mmol KCl

Schnaper HW Archives 1989
K-sparing diuretics may be superior to supplements

9 thiazide treated patients
8 4-week treatment periods
Hypokalemia in CKD

Individual level meta-analysis of 27 international cohorts
Included >1.2 million individuals for nearly 7 years

Kovesdy et al. European Heart 2018
Hypokalemia in ESRD
Prospective nationwide study
3,230 adults on dialysis
enrolled from 2008 to 2013
followed for 5 years
$K^+$ measured at enrollment, 3 mo. and q6 mo.
Mean value calculated
For HD, before treatment, for PD, random

Lee S. PlosOne 2017
Hypokalemia is a risk factor for mortality

Hemodialysis

Peritoneal dialysis

Lee S. PlosOne 2017
Hypokalemia in PD associated with risk of death

Multicentered study from DaVita
10,000 PD
111,000 HD

PD patients were younger with less DM

Similar graphs for cardiovascular events or infection
Treatment options in PD

• Dietary efforts
• K⁺ Supplements
• Spironolactone
CQI in K⁺ management in PD patients

- 84 patients, families and patient care team (RN, RD, MD) **dietary records** and education

![Graph showing percentage of patients with Hyperkalemia, Normal serum potassium, and Hypokalemia at 0m, 3m, and 6m](image-url)

Liu X. J Renal Nutrition 2009 publication 22
KCl supplementation on PD

1174 PD patients with K+ ≤ 3.5; used propensity score matching to remove selection bias and studied 338 in each group

Mortality due to all causes %

Potassium supplementation
NO potassium supplementation

Hazard ratio, 0.89 (95% CI, 0.68-1.16)
P = 0.38 by log-rank tests

Zhang Y et al. Renal Failure 2016
Publication 23
### Spironolactone in Peritoneal Dialysis

#### Table 2. Pre and post spironolactone changes by indication.

<table>
<thead>
<tr>
<th></th>
<th>Entire Population (n = 53)</th>
<th>For Hypokalemia (n = 33)</th>
<th>As a Diuretic (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>P value</td>
</tr>
<tr>
<td>K (mmol/l)</td>
<td>3.7 +/- 0.4</td>
<td>4.2 +/- 0.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Creat (mmol/l)</td>
<td>698 +/- 300</td>
<td>699.5 +/- 279</td>
<td>0.99</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>150 +/- 18</td>
<td>137 +/- 24</td>
<td>0.002</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>83.6 +/- 14.41</td>
<td>77.9 +/- 13.51</td>
<td>0.08</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>85.4 +/- 17.8</td>
<td>85.4 +/- 17.6</td>
<td>0.98</td>
</tr>
</tbody>
</table>
Hypokalemia in Hemodialysis

- In DOPPS, relatively lower serum potassium PREdialysis was not associated with all-cause mortality (these patients tended to have shorter vintage)

<table>
<thead>
<tr>
<th>Serum K (mEq/L)</th>
<th>N patients (%)</th>
<th>HR (95% CI), All-cause mortality Unadjusted</th>
<th>HR (95% CI), All-cause mortality Adjusted*</th>
<th>HR (95% CI), Arrhythmia composite^</th>
<th>HR (95% CI), Arrhythmia composite^ Adjusted^</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4.0</td>
<td>6153 (11%)</td>
<td>1.18 (1.12–1.24)</td>
<td>1.03 (0.97–1.09)</td>
<td>0.99 (0.88–1.11)</td>
<td>0.94 (0.83–1.05)</td>
</tr>
<tr>
<td>4.0 – 5.0</td>
<td>27107 (50%)</td>
<td>1 (Ref.)</td>
<td>1 (Ref.)</td>
<td>1 (Ref.)</td>
<td>1 (Ref.)</td>
</tr>
<tr>
<td>5.1 – 5.5</td>
<td>10635 (20%)</td>
<td>0.95 (0.91–0.99)</td>
<td>1.02 (0.97–1.07)</td>
<td>0.97 (0.89–1.07)</td>
<td>1.00 (0.91–1.10)</td>
</tr>
<tr>
<td>5.6 – 6.0</td>
<td>6238 (11%)</td>
<td>1.02 (0.96–1.08)</td>
<td>1.13 (1.06–1.20)</td>
<td>1.05 (0.95–1.17)</td>
<td>1.07 (0.96–1.20)</td>
</tr>
<tr>
<td>&gt; 6.0</td>
<td>4403 (8%)</td>
<td>1.00 (0.93–1.07)</td>
<td>1.12 (1.04–1.21)</td>
<td>1.16 (1.02–1.32)</td>
<td>1.21 (1.05–1.38)</td>
</tr>
</tbody>
</table>

HR: Hazard ratio; Cox models stratified by DOPPS phase, country, US large dialysis organization (all-cause mortality only), Karaboyas et al. Am J Kid Dis 2017
Post dialysis HYPOkalemia can occur
502 peri-dialytic cardiac arrest
with >90 day data available
of 43,200 DaVita patients 2002-2005
Matched with control cohort 1632