Does kayexalate have a role in the ED management of hyperkalemia?

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Problem Based Lecture
6/6/2013
Objectives

- Brief review of hyperkalemia and current treatments
- Review evidence for use of kayexalate in the treatment of hyperkalemia
- Review evidence for harm that may be caused by kayexalate
- Suggest an approach to using kayexalate in the ED
Case

- 42 year old female with history of ESRD on hemodialysis MWF, dialysis non-compliance, and recurrent small bowel obstructions s/p multiple laparotomies presents to ED with a chief complaint of weakness. She has missed her last 2 hemodialysis sessions.
EKG
Labs

6.1 | 18 | 40
---|---|---
|   | 9 |   
“Doctor, the thing that I hate the most about missing dialysis is that medicine you make me drink that hurts my stomach and gives me the runs for hours. Please doctor, is there any way I can avoid that medicine? I’ll do anything you ask me to, just please, please, please don’t make me take that. I just can’t deal with that today.”
Potassium physiology

- K⁺ is the most abundant cation in the body and plays key roles in nerve impulse conduction and muscle contraction
- 98% intracellular (140 mmol/L) and 2% extracellular (3.8 – 5.0 mmol/L)
- Long term K⁺ homeostasis mainly through renal excretion
- Daily K⁺ intake can range from 40 mmol to 200 mmol per day with little effect on serum concentration
Hyperkalemia

- Increased $K^+$ release from cells or decreased $K^+$ excretion

- Major cause of hyperkalemia is renal failure
  - Capacity to excrete $K^+$ falls off when GFR < 15-20 ml/min (normal > 90 ml/min)
  - Patients with renal failure are also more likely to be on medications that increase $K^+$ (BB, ACE, ARBs)
Management of hyperkalemia

- Stabilization of cardiac conduction
  - calcium

- Shift K from extracellular to intracellular compartment
  - Insulin
  - B2 agonist
  - Bicarb if acidotic

- Increase excretion of $K^+$
  - Loop diuretics if producing urine
  - kayexalate?
  - hemodialysis
Kayexalate: background

- Kayexalate = sodium polystyrene sulfonate (SPS)
  - Cation exchange resin; exchange Na\(^+\) for K\(^+\)
  - Given mixed with sorbitol due to constipating effect of kayexalate alone

- Most of the Na\(^+\) for K\(^+\) exchange thought to happen in the colon; thought to increase K\(^+\) elimination through increased GI loss

- Variables: contact time of resin with ion containing solution, relative concentrations of the two ions, resin capacity, extracellular potassium concentration of K\(^+\) and Na\(^+\), colonic transit time

- Approved for treatment of hyperkalemia in 1958, 4 years before Kefauver-Harris amendment (required to prove effectiveness and safety)
In late 1940s clinical consequences of “potassium intoxication” became recognized at the same time that medical uses of resins were being tested. Dialysis was not routinely done and loop diuretics were in development. Clinicians needed a way to eliminate $K^+$ in patients who didn’t produce urine. Today approximately 5 million doses given per year.
Our formulation: 15 g kayexalate in 20g sorbitol (33% sorbitol); usually administer 30 g at a time
EM textbooks on kayexalate

- Rosen’s: “To remove potassium from the body, sodium polystyrene sulfonate (Kayexalate), a resin that exchanges sodium for potassium ions, can be administered orally or rectally. This drug can continue to control the potassium for hours and, despite the modest sodium load it entails, can be effective as a temporizing measure until dialysis (if necessary) can be instituted.” (1274)

- Tittinalli: page 123, Table 21-3 – kayexalate listed as one of the emergency therapies for hyperkalemia
32 patients with renal failure: oliguric (23) and chronic (9)

All received 30-60g of kayexalate, all had low K⁺ diet
- 5 also received bicarb
- 3 also received glucose and insulin
- Oliguric patients (23) also received 600mL of 20% dextrose solution daily and high calorie diet
- 22 received orally, 2 orally over months, 8 rectally
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<td>6.6</td>
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*3 times/wk.
Results

- 30 patients had a fall in serum K\(^+\) or no increase in serum K\(^+\) at 24 hours.
- 23 patients had a fall in serum K\(^+\) of at least 0.4 mEq/L.
- Mean fall in oral group kayexalate group was 1 mEq/L vs. 0.8 meq/L in rectal kayexalate group.
- Patients 5, 9, and 18 did not receive insulin, glucose, or bicarb but became hypokalemic afterwards (7.4 to 2.3, 3.7 to 2.1, and 5.1 to 2.9).
Weaknesses

- Only 16 patients truly hyperkalemic (K⁺>5)
- 7/32 patients received other medications that can lower K⁺ (insulin, bicarb)
- Oliguric patients (23/32) received infusions of D20 and high calorie diet
  - Could increased native insulin production have been confounding?
  - Low K⁺ diet also confounding
- No control group, no statistical analysis, small number of patients
- Some patients became constipated from kayexalate and required cathartics: no data provided on which patients received cathartics
  - We will see that cathartics alone can increase fecal K⁺ loss
- 2/32 patients simply unaccounted for in final analysis– did they drop out?
- Is serum K⁺ at 24 hours relevant to the ED timeframe?

- 5/8 patients received kayexalate + sorbitol
- 3/8 patients received sorbitol alone
- For 5 days, patients’ diet was restricted to karo syrup and ginger ale (zero opportunity for K⁺ ingestion)
- Serum K⁺ checked at day 0 and day 5
  - Kayexalate with sorbitol group: K⁺ 6.6 → 5.2 (-1.4)
  - Sorbitol alone group: K⁺ 6.3 → 4.6 (-1.7)
Weaknesses

- Small number of patients
- No control group or statistical analysis
- Why did sorbitol alone cause greater K$^+$ loss than kayexalate + sorbitol?
- High calorie diet and K$^+$ restriction confounding (as in Scherr’s study)
- Is serum K$^+$ at 5 days a relevant ED outcome?

- No clear reason why sorbitol was chosen to be the laxative given with kayexalate, so authors decided to test other kayexalate-laxative combinations

- 9 normal humans without renal failure exposed to:
  - sorbitol alone
  - sorbitol plus kayexalate
  - phenolphthalein/docusate alone
  - phenolphthalein/docusate plus kayexalate
Na⁺, K⁺, and water excretion in 12 hour stool collections analyzed 24h after administration

Primary endpoint: amount of K⁺ (mEq) in stool
- Phenolphthalein/docusate-kayexalate: 49 ± 6
- Sorbitol-kayexalate: 29± 4
- Sorbitol alone: 32± 4
- Phenolphthalein/docusate alone: 37 ± 4
Weaknesses

- Small sample
- No true controls
- Again, sorbitol alone seems to be comparable or superior to sorbitol with kayexalate, as in the Flinn paper-- not discussed
- Reported no baseline fecal K⁺ loss to compare loss from laxative and laxative-kayexalate combinations
6 patients with chronic renal failure on hemodialysis underwent 5 studies on 5 different experimental days separated by 1 week.

Patients studied at 2 days after the last dialysis session and 1 day before the next dialysis session; they consumed one of the following:
- Placebo: 8 gelatin caps with 500mL water
- Kayexalate 30g with 500 mL water
- Phenolphthalein-docusate: 8 tablets with 500 mL water
- Phenolphthalein-docusate 8 tables with kayexalate 30g with 500mL water
- Sorbitol 60g plus kayexalate 30g with 500mL water
4 hours later they consumed a meal containing $21.4 \pm 1.4$ mEq of $K^+$. No other foods or beverages consumed during study.

Primary endpoints:
- Fecal $K^+$ output at 12 hours
- Change in serum $K^+$ at 12 hours
Effect of Single Dose Resin-Cathartic Therapy on Serum Potassium Concentrations in Patients with End-Stage Renal Disease. (continued)

Fecal K output (mEq/12h)

phenolphthalein: 54 + 19

phenolphthalein + kayexalate: 49 + 10

sorbitol + kayexalate: 31 + 4
Effect of Single Dose Resin-Cathartic Therapy on Serum Potassium Concentrations in Patients with End-Stage Renal Disease. (continued)

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<th></th>
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<th>Resin + sorbitol</th>
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<td>hour 0</td>
<td>4.32 ± 0.33</td>
<td>4.21 ± 0.27</td>
<td>4.24 ± 0.38</td>
<td>4.35 ± 0.26</td>
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<td>hour 4</td>
<td>4.44 ± 0.43</td>
<td>4.26 ± 0.25</td>
<td>4.60 ± 0.53</td>
<td>4.42 ± 0.41</td>
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<td>hour 8</td>
<td>4.57 ± 0.34</td>
<td>4.29 ± 0.29</td>
<td>4.50 ± 0.38</td>
<td>4.57 ± 0.43</td>
<td>4.30 ± 0.42</td>
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<td>hour 12</td>
<td>4.71 ± 0.35</td>
<td>4.29 ± 0.27</td>
<td>4.62 ± 0.50</td>
<td>4.65 ± 0.42</td>
<td>4.28 ± 0.43</td>
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*Note: We were not able to obtain a blood sample at all of the four phenolphthalein alone. Therefore, none of his serum values was verifiable. Individual results for serum potassium concentration on all...*
GI loss of $K^+$ due to kayexalate and laxatives may not be significant in comparison to total $K^+$ in the body.

“Because single-dose resin-cathartic therapy produces no or only trivial reductions in serum potassium concentration, and because this therapy is unpleasant and occasionally is associated with serious complications, this study questions the wisdom of its use in the management of acute hyperkalemic episodes.”
Weaknesses

- Did not report data on fecal $K^+$ output in the placebo and kayexalate-alone groups
- Data from 1/6 patients was lost due to difficulty obtaining blood samples
- Small study

- Retrospective cohort study reviewing EMRs of inpatients receiving kayexalate for hyperkalemia (K⁺ > 5.1) at Jessie Brown VA Medical Center from 1/1/2006 - 12/31/2006
- Mean serum Cr of 2.57 ± 2.36 mg/dL
- Primary endpoint: mean change in serum K⁺ concentration associated with kayexalate administration at an average of 10 hours after administration
- Exclusion criteria: chronic kayexalate use, multiple doses, current hemodialysis, other treatments for hyperkalemia (insulin, dextrose, albuterol, furosemide)
- 140 patients met identified, 122 patients met inclusion criteria. 4 different kayexalate dosages:
  - 15g group (30 pts) mean K⁺: 5.40 ± 0.18
  - 30g group (60 pts) mean K⁺: 5.51 ± 0.30
  - 45g group (19 pts) mean K⁺: 5.83 ± 0.46
  - 60g group (13 pts) mean K⁺: 5.92 ± 0.30
Results: Mean reduction in serum $K^+$ Concentration (mEq/L) by Group

- 15g kayexalate: - 0.82
- 30g kayexalate: - 0.95
- 45g kayexalate: - 1.11
- 60g kayexalate: - 1.4
Weaknesses

- Retrospective chart review
  - No control
  - Unknown confounders
  - Incomplete documentation
  - 99% of the patients were men
  - Population was limited to VA inpatients

- Retrospective cohort analysis of all hospitalized patients who received kayexalate over 4 months (1/1/2010 – 4/30/2010)

- Primary endpoint: change in serum $K^+$ at 24 hours after administration of kayexalate

- Exclusion criteria: age < 18, current dialysis, other treatments for hyperkalemia (insulin, dextrose, albuterol, furosemide), $K^+$ supplementation, $K^+$ below 5 or greater than 7

- Kayexalate given to 312 patients, 135 met inclusion criteria
Results

- Initial mean $K^+ 5.59 \pm 0.45$ and mean $Cr 2.34 \pm 1.95$
- Overall $K^+$ decrease: 16.7% compared to baseline measurement with nadir at 16-24 hours
- $Cr$ was stable over time, suggesting that improved renal function did not account for decrease in $K^+$
Weaknesses

- Retrospective chart review
  - No controls
  - Confounders
  - Incomplete documentation
  - Inpatients, not ED patients
Only one study (Gruy-Kapral 1998) included in the Cochrane Review

- No differences in serum K⁺ at 4 hours when kayexalate compared with placebo
- Can reach no conclusions about timing of kayexalate action from this paper

Conclusions

- No randomized evidence to support use of potassium-exchange resins
- Kayexalate safe in the absence of GI pathology, may be used for their “possible” effects at 24 hours, but should not be relied upon for rapid effects
Potential for Harm

- Hundreds of case reports associating kayexalate-sorbitol administration with GI adverse events: colonic necrosis, perforation

- 70% sorbitol mixed with kayexalate has been blamed:
  - A case report of a patient who died of colonic necrosis after getting kayexalate-sorbitol noticed a similar lesion (on path analysis) in colons of rats given enemas with 70% sorbitol, with or without kayexalate, but not with enemas of kayexalate alone → 2006 FDA stopped recommending formulations with 70% sorbitol
  - Carolina Medical, manufacturer of kayexalate-sorbitol in the US, had never received an adverse event report with the 33% sorbitol formulation, so FDA has allowed them to continue to market 33% formulation
  - Bizarrely, 70% sorbitol still available as an over-the-counter laxative

- Identified 553 relevant articles from literature search
- Included cases had to meet WHO-UMC causality criteria for possible causal link between kayexalate and adverse GI events
<table>
<thead>
<tr>
<th>Causality term</th>
<th>Assessment criteria</th>
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| Certain              | • Event or laboratory test abnormality, with plausible time relationship to drug intake  
• Cannot be explained by disease or other drugs  
• Response to withdrawal plausible (pharmacologically, pathologically)  
• Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon)  
• Rechallenge satisfactory, if necessary |
| Probable/Likely      | • Event or laboratory test abnormality, with reasonable time relationship to drug intake  
• Unlikely to be attributed to disease or other drugs  
• Response to withdrawal clinically reasonable  
• Rechallenge not required |
| Possible             | • Event or laboratory test abnormality, with reasonable time relationship to drug intake  
• Could also be explained by disease or other drugs  
• Information on drug withdrawal may be lacking or unclear |
| Unlikely             | • Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)  
• Disease or other drugs provide plausible explanations |
| Conditional/Unclassified | • Event or laboratory test abnormality  
• More data for proper assessment needed, or  
• Additional data under examination |
| Unassessable/Unclassifiable | • Report suggesting an adverse reaction  
• Cannot be judged because information is insufficient or contradictory  
• Data cannot be supplemented or verified |

*All points should be reasonably complied with
Reviewed 30 reports describing 58 cases (41 preparations of kayexalate with sorbitol and 17 with kayexalate alone)

Colon was most common site of injury with transmural necrosis the most common histopathological lesion (36), injury also found in stomach, esophagus in some cases

16 cases were post-operative patients

91% of cases had history of AKI, CKD, or ESRD
Weaknesses

- Review of case reports
- No idea about incidence
- Multiple possible confounders
  - Patients with renal failure often have pre-existing vascular disease; elevated renin levels predispose to mesenteric ischemia; post-op patients can have hemodynamics that predispose to mesenteric ischemia; medications like opiates decrease gut motility
“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.”
In response to Sterns: “We feel these conclusions are immoderate.”

“SPS has an important role in the treatment of hyperkalemic under austere conditions… and as a prophylaxis in dialysis-dependent patients who are not able to get to a dialysis unit… In our experience, oral SPS/sorbitol is a useful and effective medication, and existing studies [citing 1961 Scherr paper] in subjects with hyperkalemia support its efficacy. We can find no studies that demonstrate that it is ineffective [generous interpretation of Gruy-Kapral] in lowering potassium in patients with hyperkalemia after 8 to 24 hours of treatment.”
“Decisions regarding the continued use of SPS resins should take into account the historical context in which they were developed, the efficacy data that is available, the reasons for the addition of cathartic agents, and a calm assessment of the patient profile most likely to be associated with serious side effects, especially colonic necrosis. Death from hyperkalemia is an unacceptable outcome. We have no data estimating the number of adverse events (hyperkalemic arrest, hospitalization, and need for acute dialysis) averted by SPS resin use, and thus it is not possible to decide whether the risks of colonic necrosis outweigh the benefits. Until there is better evidence of excess harm, or a better agent available for increasing potassium excretion, we should continue to use SPS when it is indicated. It is unwise to create a climate in which a physician attempting to control hyperkalemia can be accused of malpractice if SPS is used and if it is not.”
42 year old female with history of ESRD on hemodialysis MWF, dialysis non-compliance, and recurrent small bowel obstructions s/p multiple laparotomies presents to ED with a chief complaint of weakness. She has missed her last 2 hemodialysis sessions.
Conclusions

- Evidence for ED use of kayexalate for acute hyperkalemia is weak
  - Calcium acts immediately and lasts 30 – 60 min
  - Insulin/glucose takes effect in 10-15 minutes and lasts 4-6 hours
  - We can check labs and EKGs quickly and re-dose as needed

- There is some evidence that kayexalate lowers potassium, though not in a timeframe immediately relevant to the ED
  - 10 hours seems to be the earliest time for which there may be benefit
Conclusions, continued

- If kayexalate were developed today, it would not be used in the ED management of hyperkalemia based on existing data.

- Evidence for harm from kayexalate appears small when compared to number of doses of kayexalate given yearly, but we have no clear idea about incidence and there are probably certain patient populations who should avoid it.

- With the limits of current data, the decision to give or withhold kayexalate must be made in the context of available resources, patient status, who you are handing patient off to, institutional factors, etc.


