The “Attraction” of Phosphate Binders in Chronic Kidney Disease

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NMSHP Fall 2014

Learning Objectives

• Pharmacist
  1. Describe the role of phosphate binders in chronic kidney disease related mineral and bone disorder.
  2. Compare and contrast the different classes of phosphate binders.
  3. Discuss major safety issues associated with each class of phosphate binders.
  4. Select an appropriate phosphate binder(s) for patients with chronic kidney disease.

• Pharmacy Technician
  1. Explain the indication for phosphate binders.
  2. Identify agents used for phosphate binding.
  3. Specify available phosphate binder dosage forms.
Types of Renal Bone Disorders

- Osteitis fibrosis cystica
  - Excess PTH
  - Bone marrow fibrosis

- Osteomalacia
  - Defective mineralization
  - Vitamin D deficiency, (Al toxicity)

- Adynamic bone disease
  - Cause? Associated with lower levels of PTH

- Mixed uremic osteodystrophy
Coronary Calcification

http://www.daviddarling.info/encyclopedia/C/coronary_calcium_scan.html

Soft Tissue Calcification

Figure 15. Metastatic calcification of the lungs.

Images courtesy of Eduardo Slatopolsky, MD.
Soft Tissue Calcification

In an autopsy study of 56 patients who died while undergoing chronic dialysis and 18 nondialyzed patients with CRF, extraskeletal calcification was found in 79% of dialysis patients and 44% of nondialyzed patients. Severe, generalized visceral lesions were present in 36% of dialysis patients and 11% of nondialyzed patients (Table 6). Severe calcification of the cardiac conduction system or myocardium was concluded to be the cause of death in 6 patients.

Soft Tissue Calcification

Periarticular Calcification and Generalized Calcification

Periarticular (Figures 17 and 18), ocular, and cutaneous calcification may likewise accompany kidney disease and contribute to patient morbidity, further decreasing patient mobility and quality of life.

Figure 17. Periarticular metastatic calcification, hand.

A 24-year-old patient with chronic renal disease presented with pain and swelling in the joints of her hands. Photographs depict periarticular calcifications. With control of her serum phosphates levels the calcifications decreased but failed to completely resolve. Periarticular calcifications are often visible radiologically but are usually asymptomatic. However, they may progress to digital deposits, produce arthritic arthritis, or limit the range of motion of affected joints.

Photographs from Scharff M. Am J Med.
Calciphylaxis

Case 1 – T. S. 61 y.o. female

- PMH
  - DM Type 2
  - HTN
  - CKD
- Meds
  - Ramipril 5 mg PO daily
  - Ferrous fumarate 300 mg PO TID
  - Lantus 24 U SC daily
  - Humalog TIDcc
- PE
  - 1+ bilateral edema

- Labs
  - SCr 1.5 mg/dL
  - eGFR 33 mL/min/1.73m²
  - Ca 9.2 mg/dL (8.4-10.4)
  - P 6.7 mg/dL (2.3-5.6)
  - iPTH 314 pg/mL (11-80)
CKD Mineral and Bone Disorder Guidelines

- KDIGO (Kidney Disease Improving Global Outcomes)
  - [http://kdigo.org/home/mineral-bone-disorder/](http://kdigo.org/home/mineral-bone-disorder/)

- KDOQI (Kidney Disease Outcomes Quality Initiative)

CHRONIC KIDNEY DISEASE (CKD)

- ↓ P elimination
- ↓ Vitamin D activation
- ↓ serum P
- ↑ serum Ca
- ↑ PTH secretion
- Parathyroid Hyperplasia
- Secondary Hyperparathyroidism
- RENAL BONE DISORDERS
- ↑ Ca reabsorption
- ↓ P Reabsorption

Phosphate Binders
- Vitamin D Analogs
- Calcimimetic

(Kidneys) Vitamin D activation
Bone Resorption
↑ serum Ca
↑ serum P
SOFT TISSUE CALCIFICATION
### Guideline Recommendations

<table>
<thead>
<tr>
<th>Phosphorus</th>
<th>KDIGO</th>
<th>KDOQI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 3 (GFR 30-59)</td>
<td>Normal serum P</td>
<td>2.7-4.6 mg/dL</td>
</tr>
<tr>
<td>Stage 4 (GFR 15-29)</td>
<td>Normal serum P</td>
<td>2.7-4.6 mg/dL</td>
</tr>
<tr>
<td>Stage 5ND (GFR &lt;15)</td>
<td>Normal serum P</td>
<td>3.5-5.5 mg/dL</td>
</tr>
<tr>
<td>Stage 5D (PD/HD)</td>
<td>Lower towards normal serum P range</td>
<td>3.5-5.5 mg/dL</td>
</tr>
</tbody>
</table>

### Guideline Recommendations

<table>
<thead>
<tr>
<th>Calcium</th>
<th>KDIGO</th>
<th>KDOQI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 3 (GFR 30-59)</td>
<td>Normal serum Ca</td>
<td>Normal serum Ca</td>
</tr>
<tr>
<td>Stage 4 (GFR 15-29)</td>
<td>Normal serum Ca</td>
<td>Normal serum Ca</td>
</tr>
<tr>
<td>Stage 5ND (GFR &lt;15)</td>
<td>Normal serum Ca</td>
<td>Normal serum Ca range, preferably lower end (8.4-9.5 mg/dL)</td>
</tr>
<tr>
<td>Stage 5D (PD/HD)</td>
<td>Normal serum Ca</td>
<td>Normal serum Ca range, preferably lower end (8.4-9.5 mg/dL)</td>
</tr>
</tbody>
</table>
Dietary Phosphorus Restriction

- Beverages:
  - Ale
  - Beer
  - Cocoa
  - Dark colas
- Dairy products:
  - Cheese
  - Ice cream
  - Milk
  - Cream soups
  - Yogurt
- Protein:
  - Carp
  - Fish roe
  - Organ meets
  - Oysters
  - Sardines
- Dried beans & peas
- Others:
  - Bran cereals
  - Whole grain products
  - Nuts

Phosphate Binders

<table>
<thead>
<tr>
<th></th>
<th>Rx</th>
<th>Formulations</th>
<th>Place in Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum hydroxide</td>
<td>No</td>
<td>Liquid, tablet, capsule</td>
<td>Alternate</td>
</tr>
<tr>
<td>Calcium-based</td>
<td></td>
<td></td>
<td>Preferred</td>
</tr>
<tr>
<td>Ca acetate</td>
<td>Yes/no</td>
<td>Capsule, tablet</td>
<td></td>
</tr>
<tr>
<td>Ca carbonate</td>
<td>No</td>
<td>Liquid, tablet, chewable, capsule</td>
<td></td>
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<tr>
<td>Lanthanum carbonate</td>
<td>Yes</td>
<td>Chewable tablet</td>
<td>Alternate</td>
</tr>
<tr>
<td>Sevelamer</td>
<td></td>
<td></td>
<td>Preferred</td>
</tr>
<tr>
<td>Sevelamer HCl (Renagel)</td>
<td>Yes</td>
<td>Tablet</td>
<td></td>
</tr>
<tr>
<td>Sevelamer carbonate (Renvela)</td>
<td>Yes</td>
<td>Tablet, powder</td>
<td></td>
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</tbody>
</table>
Biochemical Endpoints

<table>
<thead>
<tr>
<th></th>
<th>SVR (n=99)</th>
<th>Ca (n=101)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>5.1±1.2</td>
<td>5.1±1.4</td>
<td>NS</td>
</tr>
<tr>
<td>Ca</td>
<td>9.5±0.6</td>
<td>9.7±0.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>↑Ca</td>
<td>5%</td>
<td>16%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>iPTH</td>
<td>224</td>
<td>138</td>
<td>NS</td>
</tr>
<tr>
<td>↓iPTH</td>
<td>30%</td>
<td>57%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TC</td>
<td>141±28</td>
<td>182±49</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LDL</td>
<td>65±21</td>
<td>103±43</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HDL</td>
<td>43±10</td>
<td>45±12</td>
<td>NS</td>
</tr>
<tr>
<td>Trig</td>
<td>137</td>
<td>150</td>
<td>NS</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th></th>
<th>SVR (n=54)</th>
<th>Ca (n=55)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>5.2±0.9</td>
<td>5.1±0.8</td>
<td>NS</td>
</tr>
<tr>
<td>Ca</td>
<td>9.1±0.5</td>
<td>9.6±0.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>iPTH</td>
<td>298±152</td>
<td>243±16</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>↓iPTH</td>
<td>30%</td>
<td>57%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TC</td>
<td>134±52</td>
<td>160±32</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LDL</td>
<td>60±34</td>
<td>81±26</td>
<td>&lt;0.05</td>
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<tr>
<td>Trig</td>
<td>171±108</td>
<td>191±106</td>
<td>NS</td>
</tr>
</tbody>
</table>


Bone Histology Summary

- No major difference between calcium carbonate with lanthanum carbonate or sevelamer
- Changes in bone turnover were heterogenous
  - Some patients improved while others worsened
- Results influenced by baseline turnover rates

Treat to Goal

Sevelamer vs Calcium

Coronary Artery Calcification

Aortic Calcification

RIND

- CAC = 0 at baseline, none progressed to CAC >30 by study end
- CAC >30 at baseline, progressive CAC increase (in sevelamer and Ca arm)
- Ca arm: more rapid and severe increase in CAC

<table>
<thead>
<tr>
<th></th>
<th>Baseline CAC = 0 (n=37)</th>
<th>Baseline CAC &gt;0 (n=72)</th>
<th>P&lt;0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>45 ± 12 y</td>
<td>64 ± 11 y</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

RIND

- During parent study, subjects remained on their assigned phosphate binder (sevelamer vs calcium)
- After final scan, subjects given phosphate binders at discretion of primary nephrologist
- Median follow up = 44 months


RIND Follow up

![Graph showing survival distribution function with P=0.002.]

Adjusted (age, race, gender, diabetes)

RIND Follow up

Adjusted (age, race, gender, DM, history artherosclerotic cardiovascular disease, CRP, albumin, Kt/V, baseline CAC)


DCOR

- Prospective, multi-center, randomized, open-labeled, parallel design
- Adult HD (>3 mo)
- Required phosphate binder
- Medicare = primary insurance
- Powered to detect all-cause mortality

## DCOR

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Sevelamer (n=99)</th>
<th>Calcium (n=101)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P</strong></td>
<td>5.8±1.3</td>
<td>5.7±1.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Ca</strong></td>
<td>9.2±0.7</td>
<td>9.5±0.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>iPTH, median</td>
<td>278 (200,476)</td>
<td>226 (142,387)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>TC</strong></td>
<td>146±34</td>
<td>161±35</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>LDL</strong></td>
<td>69±26</td>
<td>85±31</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>HDL</strong></td>
<td>45±15</td>
<td>44±16</td>
<td>NS</td>
</tr>
</tbody>
</table>

All-cause Mortality: 
P = 0.40  
Cardiovascular Mortality: 
P = 0.53

Calcium = black line  
Sevelamer = green line

DCOR Patient disposition

Randomized (N=2103)

Sevelamer (N=1053)
- D/C (N=502)
- A/E (N=81)
- Completed (N=551)

Calcium (N=1050)
- D/C (N=533)
- A/E (N=50)
- Completed (N=517)

DCOR Secondary Analysis

CMS Data

Randomized
N=2103

Linked to CMS database
N=2101

Mortality
N=2101

Sevelamer
N=1051
Completed
N=938

Calcium
N=1050
Completed
N=938

Morbidity/Hospitalization
N=1947

Sevelamer
N=979
Completed
N=735

Calcium
N=968
Completed
N=735


DCOR Secondary Analysis

• All-cause mortality

• Cardiovascular mortality = NS

### DCOR Secondary Analysis

<table>
<thead>
<tr>
<th></th>
<th>Sevelamer (N=979)</th>
<th>Calcium (N=968)</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Hospitalization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted RR</td>
<td>0.98</td>
<td>Reference</td>
<td>0.89-1.08</td>
<td>0.7</td>
</tr>
<tr>
<td>Adjusted RR</td>
<td>0.99</td>
<td>Reference</td>
<td>0.90-1.09</td>
<td>0.9</td>
</tr>
<tr>
<td>Multiple hospitalizations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted RR</td>
<td>0.90</td>
<td>Reference</td>
<td>0.82-0.99</td>
<td>0.03</td>
</tr>
<tr>
<td>Adjusted RR</td>
<td>0.89</td>
<td>Reference</td>
<td>0.82-0.98</td>
<td>0.02</td>
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<tr>
<td>Hospital days</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Unadjusted RR</td>
<td>0.88</td>
<td>Reference</td>
<td>0.78-1.00</td>
<td>0.05</td>
</tr>
<tr>
<td>Adjusted RR</td>
<td>0.88</td>
<td>Reference</td>
<td>0.78-0.99</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Adjusted (age, race, sex, dialysis vintage, DM, comorbid cardiovascular conditions)


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### CARE-2

- Multicenter, randomized, controlled, open-label, non-inferiority trial
- Assess calcification progression in HD patients treated with calcium-containing vs calcium-free phosphate binders when LDL-C was decreased to <70 mg/dL.
  - P >5.5 mg/dL
  - LDL >80 mg/dL
  - CAC scores 30 to 7000 Units at baseline
- Ca acetate n=103; sevelamer n=100
  - P goal 3.5 to 5.5
  - Atorvastatin added to achieve LDL <70 mg/dL in both groups

## CARE-2

<table>
<thead>
<tr>
<th></th>
<th>Sevelamer (n=70)</th>
<th>Calcium (n=59)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>5.4±1.8</td>
<td>5.0±1.6</td>
<td>NSD</td>
</tr>
<tr>
<td>Ca</td>
<td>9.0±0.7</td>
<td>9.4±0.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>iPTh</td>
<td>434±359</td>
<td>316±212</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>TC</td>
<td>126±30.6</td>
<td>134±32.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LDL</td>
<td>62.4±23.0</td>
<td>68.8±22.3</td>
<td>NS</td>
</tr>
<tr>
<td>HDL</td>
<td>38.8±11.3</td>
<td>36.4±8.7</td>
<td>NS</td>
</tr>
<tr>
<td>Trig</td>
<td>149±69.8</td>
<td>157±124</td>
<td>NS</td>
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</tbody>
</table>


## CARE-2 CAC Scores

<table>
<thead>
<tr>
<th></th>
<th>Sevelamer</th>
<th>Calcium Acetate</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline CAC</td>
<td>969±1,386</td>
<td>1,098±1,440</td>
<td>NS</td>
</tr>
<tr>
<td>6 mo CAC</td>
<td>996±1,419</td>
<td>1,197±1,413</td>
<td>NS</td>
</tr>
<tr>
<td>6 mo absolute increase</td>
<td>97±211 (p&lt;0.0001)</td>
<td>109±374 (p&lt;0.0001)</td>
<td>NS</td>
</tr>
<tr>
<td>6 mo % increase</td>
<td>24±39</td>
<td>71±365</td>
<td>NS</td>
</tr>
<tr>
<td>12 mo CAC</td>
<td>1,116±1,569</td>
<td>1,297±1,487</td>
<td>NS</td>
</tr>
<tr>
<td>12 mo absolute increase</td>
<td>227±485 (p&lt;0.0001)</td>
<td>228±355 (p&lt;0.0001)</td>
<td>NS</td>
</tr>
<tr>
<td>12 mo % increase</td>
<td>57±86</td>
<td>52±92</td>
<td>NS</td>
</tr>
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</table>

Lanthanum Carbonate

- Effectively lowers serum phosphorous and iPTH
- Does not increase serum Ca
- Adverse effect rates comparable to other phosphate binders
- Accumulation in blood and bone below toxic levels
  - Studies were short in duration, most ≤ 1y


Aluminum Hydroxide

- Al adverse effects:
  - Central nervous system toxicity (Dialysis Dementia)
  - Osteomalacia
  - Microcytic anemia
  - Citrate increases intestinal Al absorption
  - KDIGO Guidelines: Avoid long-term use
  - KDOQI: May be used as short-term therapy (4 wk) in patients with serum P >7 mg/dL
  - Safe quantity of Al phosphate binder unknown
## Phosphate Binders

<table>
<thead>
<tr>
<th></th>
<th>Rx</th>
<th>Cost</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum hydroxide</td>
<td>No</td>
<td>$10/500 mL</td>
<td>Al content varies 100 to &gt;200 mg (per tablet)</td>
</tr>
<tr>
<td>Calcium-based</td>
<td></td>
<td></td>
<td>KDOQI recommends not to exceed 2000 mg/day elemental Ca</td>
</tr>
<tr>
<td>Ca acetate</td>
<td>Yes/no</td>
<td>$100/100 tablets</td>
<td>Medicaid formulary 25% elemental Ca</td>
</tr>
<tr>
<td>Ca carbonate</td>
<td>No</td>
<td>$10/100 tablets</td>
<td>40% elemental Ca</td>
</tr>
<tr>
<td>Lanthanum carbonate</td>
<td>Yes</td>
<td>$990/100 tablets</td>
<td></td>
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<tr>
<td>Sevelamer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sevelamer HCl (Renagel)</td>
<td>Yes</td>
<td>$530/100 tablets</td>
<td>Medicaid formulary ↓ Ciprofloxacin absorption *50%</td>
</tr>
<tr>
<td>Sevelamer carbonate (Renvela)</td>
<td>Yes</td>
<td>$430/100 tablets</td>
<td></td>
</tr>
</tbody>
</table>

## Pipeline – Resin

- **Colestilan (MCI-196)**
  - Anion exchange resin
    - Effective phosphate and cholesterol lowering
Pipeline – Iron based

• Sucroferric oxyhydroxide (PA21)
    • Equivalent phosphate control with 3 pills/day compared to 8 of sevelamer

• Ferric Citrate (JTT-751)
    • Effective phosphate binding
    • Increased iron stores, decreased IV iron and erythropoietin administration

Case 1 – T. S. 61 y.o. female

• PMH
  • DM Type 2
  • HTN
  • CKD
• Meds
  • Ramipril 5 mg PO daily
  • Ferrous fumarate 300 mg PO TID
  • Lantus 24 U SC daily
  • Humalog TIDcc
• PE
  • 1+ bilateral edema

• Labs
  • SCr 1.5 mg/dL
  • eGFR 33 mL/min/1.73m²
  • Ca 9.2 mg/dL (8.4-10.4)
  • P 6.7 mg/dL (2.3-5.6)
  • iPTH 314 pg/mL (11-80)
Case 2 – QQ 54 y.o. female

- Receives hemodialysis MWF
- Medications:
  - CaCO₃ 1250 mg PO TIDcc & snacks
  - Epoetin alpha 4000 U with HD
  - Iron sucrose 100 mg IV q week
  - Renal vitamin PO daily

What is the most appropriate change to recommend?

A. Increase CaCO₃ to 2.5 g TIDcc & snacks
B. D/C CaCO₃, start Ca acetate 667 mg TIDcc & snacks
C. D/C CaCO₃, start AlOH₃ 320 mg TIDcc & snacks
D. D/C CaCO₃, start sevelamer carbonate 800 mg TIDcc & snacks

<table>
<thead>
<tr>
<th>Time</th>
<th>iPTH</th>
<th>Serum Ca</th>
<th>Serum P</th>
<th>Serum albumin</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mo ago</td>
<td>890</td>
<td>8.5</td>
<td>6.5</td>
<td></td>
</tr>
<tr>
<td>2 mo ago</td>
<td>744</td>
<td>8.6</td>
<td>6.8</td>
<td></td>
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<tr>
<td>Last month</td>
<td>789</td>
<td>8.5</td>
<td>7.2</td>
<td></td>
</tr>
<tr>
<td>Today</td>
<td>943</td>
<td>8.9</td>
<td>6.9</td>
<td>2</td>
</tr>
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