Management of Secondary Hyperparathyroidism in Patients with Chronic Kidney Disease

Bishoy Luka, Pharm.D., BCNSP
Clinical Pharmacist - Critical Care
Kingsbrook Jewish Medical Center
Assistant Clinical Professor of Pharmacy Practice
Arnold & Marie Schwartz College of Pharmacy
And Health Sciences, Long Island University
Brooklyn, New York

Pathogenesis of Hyperparathyroid (PTH) In Chronic Kidney Disease (CKD)

- Parathyroid gland regulates mineral metabolism
  - Calcium
  - Phosphorus
  - Vitamin D

Spectrum of Bone Disease in ESRD

- Mineral metabolism in bone may cause different types of bone disease
- Adynamic bone disease
  - TPN, calcium phosphate binders, vitamin D analogs
- Osteomalacia
- Osteitis

Urinary System

- Composed of
  - Two kidneys
  - Two ureters
  - One bladder
  - One urethra
- Nephrons: functional units
  - Site of filtration and reabsorption
- Two vital functions are performed:
  - 1. Urine is produced for excretion
  - 2. Water and electrolytes are regulated

Other Functions of the Kidney

- Endocrine
  - 1-Hydroxylation of vitamin D
  - Erythropoietin production
  - Renin production
- Metabolic
  - Glycogen storage (minor role)
- Drug removal

Kidney Damage
- Hypocalcaemia, anemia
- Impaired drug removal
- Acute phase changes

Diseases of the Urinary System

- Type 2 diabetes
  - Leading cause of chronic kidney failure
- Other conditions:
  - Kidney stones
  - Polycystic kidney disease
  - Renal Carcinoma or malignancy
  - UTT's—urinary tract infections
  - Cystitis (bladder infections)
Operational Definition of CKD

Pathogenesis of Hyperparathyroid In CKD
- Renal insufficiency >> ↓ Calcitriol (active Vitamin D)
  - Calcitriol binds to vitamin D receptors (VDR)
  - ↓ Active Vitamin D >> ↓ Ca²⁺ absorption
- Renal insufficiency >> phosphate retention
  - ↑ Phosphate >> PTH secretion
  - PTH secretion >> ↑ Ca²⁺
  - ↑ Ca²⁺ in serum leads to ↓ Ca²⁺ in bone

The Prevalence of End Stage Renal Disease
National Kidney Foundation Classification of Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR (ml/min/1.73 m²)</th>
<th>Serum Creatinine (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>90-129</td>
<td>0.6-1.3</td>
</tr>
<tr>
<td>2</td>
<td>60-89</td>
<td>1.4-2.5</td>
</tr>
<tr>
<td>3</td>
<td>30-59</td>
<td>3.5-5.5</td>
</tr>
<tr>
<td>4</td>
<td>15-29</td>
<td>6.5-8.4</td>
</tr>
<tr>
<td>5</td>
<td>&lt;15</td>
<td>8.5-10.9</td>
</tr>
</tbody>
</table>

High Serum Phosphorous Levels Are Associated with Increased Mortality


High Serum Calcium Levels are Associated Increased Mortality

High Calcium-Phosphorus Product is Associated with an Increase in Mortality

Relative Risk of Mortality by Serum Parathyroid Hormone

Cardiovascular Events and Death Associated with Progressive Renal Disease
KDOQI™ Clinical Practice Guidelines For Bone Metabolism and Disease in ESRD

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>GFR Range (mL/min)/1.73 m²</th>
<th>Phosphorus (mg/dL)</th>
<th>Corrected Calcium (mg/dL)</th>
<th>Ca x P (mg²/mL²)</th>
<th>Intact PTH (pg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>30–59</td>
<td>2.7–4.6</td>
<td>8.4–10.2</td>
<td></td>
<td>25–70</td>
</tr>
<tr>
<td>4</td>
<td>15–29</td>
<td>2.7–4.6</td>
<td>8.4–10.2</td>
<td></td>
<td>70–110</td>
</tr>
<tr>
<td>5*</td>
<td>&lt;15, dialysis</td>
<td>3.5–5.5</td>
<td>8.4–9.5</td>
<td>&lt;55</td>
<td>150–300</td>
</tr>
</tbody>
</table>

Am J Kidney Dis 2004; 43: S1 – S201

The Ability to Achieve KDOQI™ Guidelines for Mineral Metabolism is Poor

<table>
<thead>
<tr>
<th></th>
<th>Percent of Patients Within Guideline Ranges</th>
</tr>
</thead>
<tbody>
<tr>
<td>All 4</td>
<td></td>
</tr>
<tr>
<td>At least 3</td>
<td></td>
</tr>
<tr>
<td>At least 2</td>
<td></td>
</tr>
<tr>
<td>At least 1</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>


Achieving KDOQI™ Targets for Mineral Metabolism is Associated with Lower Mortality

**Goals of Therapy**

- **Immediate**
  - Maintain PTH within appropriate targets
  - Prevent parathyroid gland hyperplasia
  - Maintain normal serum phosphorus levels
  - Maintains normal serum calcium levels
  - Maintain normal skeletal function

- **Long-term**
  - Reduce risk of renal osteodystrophy
  - Reduce risk of CV morbidity and mortality

**Conventional Therapeutic Approaches**

- Control PTH and Ca
  - Vitamin D sterols
  - Ca supplements/dialysate Ca

- Control P
  - Dietary P restriction
  - Phosphate binders
Managing Hyperphosphatemia

**Dietary**
- Dialysis
- Conventional
- Nocturnal
- Restrict vitamin D
- Correct Hyperparathyroidism
  - Calcimimetics
  - Parathyroidectomy

**Binders**
- Aluminum
- Calcium salts
- Carbonate Acetate
- Sevelamer HCL
- Lanthanum

---

**AAKP NUTRITION COUNTER**

A Reference For The Kidney Patient

---

**Food** | **Portion** | **NA** | **K** | **Phos** | **Protein** | **Calorie**
--- | --- | --- | --- | --- | --- | ---

| Fruit punch, from concentrate | 8 oz | 12 | 191 | 0 | 0.2 | 124 |
| Carrot, lemon slice | 8 oz | 96 | 32 | * | 0.1 | 58 |
| Gelatin, unflavored | 1/2 cup | 56 | 0 | 32 | 1.3 | 8 |
| Gelatin, apple | 1/2 cup | 57 | 1 | 30 | 1.6 | 80 |
| Grape juice | 8 oz | 8 | 334 | 28 | 1.4 | 154 |
| Granola | 1 medium | 0 | 318 | 23 | 1.4 | 74 |
| Grapefruit juice | 8 oz | 2 | 378 | 27 | 1.3 | 94 |
| Grapes | 1 cup | 2 | 176 | 9 | 0.6 | 62 |
| Gravy, beef, canned | 10.3 oz | 1630 | 236 | 87 | 10.9 | 154 |
| Gravy, chicken, canned | 10.3 oz | 1714 | 325 | 86 | 5.8 | 135 |
| Guacamole | 1/2 cup | 240 | 180 | 1 | 0.7 | 90 |
| Guava | 1 medium | 3 | 256 | 33 | 0.7 | 46 |
| Ham, lean, round | 3 oz | 112 | 269 | 103 | 21.3 | 133 |
| Honey, drained | 1 tbsp | 0 | 1 | 0.1 | 64 |
| Honeydew | 1 cup | 18 | 480 | 18 | 0.8 | 62 |
| Hot dog, beef | 1 hot dog | 490 | 67 | 69 | 4.8 | 141 |
| Hot dog, pork | 1 hot dog | 620 | 201 | 130 | 9.7 | 204 |
| Hot dog, turkey | 1 hot dog | 642 | 81 | 60 | 6.4 | 102 |
| Ice Cream, Brey's Grand Light | 1/2 cup | 31 | * | * | 2.9 | 121 |
| Jelly | 1 tbsp | 5 | 12 | 1 | 0 | 54 |
| Ketchup | 1 tbsp | 178 | 77 | 6 | 0.2 | 15 |
| Kefirfruit | 1 medium | 4 | 252 | 30 | 0.8 | 46 |
| Lamb, leg, lean, roasted | 3 oz | 38 | 287 | 173 | 24.1 | 162 |
| Lamb, loin, brined | 3 oz | 71 | 320 | 192 | 25.5 | 184 |
| Lamb, loin, roasted | 3 oz | 56 | 227 | 173 | 24.5 | 172 |
| Lemon | 1 medium | 1 | 80 | 9 | 0.6 | 17 |
| Lemon juice | 2 tbsp | 6 | 30 | 2 | 0.2 | 4 |
Phosphorous in Dietary Protein

<table>
<thead>
<tr>
<th>Dietary Protein Intake</th>
<th>Dietary Phosphorous</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2 g/kg</td>
<td>1353 ± 253 mg</td>
</tr>
<tr>
<td>1.0 – 1.2</td>
<td>1052 ± 219 mg</td>
</tr>
<tr>
<td>0.8 – 1.0</td>
<td>936 ± 217 mg</td>
</tr>
<tr>
<td>0.6 – 0.8</td>
<td>831 ± 142 mg</td>
</tr>
<tr>
<td>&lt;0.6</td>
<td>599 ± 105 mg</td>
</tr>
</tbody>
</table>


Dialysis Phosphorus Removal: Three Times per Week

<table>
<thead>
<tr>
<th>Diet</th>
<th>1000 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>7000 mg</td>
</tr>
<tr>
<td>Dialysis</td>
<td>800 mg</td>
</tr>
<tr>
<td>Balance</td>
<td>1800 mg</td>
</tr>
</tbody>
</table>

Phosphorus in Dietary Protein

Dialysis Phosphorus Removal: Six Times per Week

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet</td>
<td>1000 mg/day</td>
<td>7000 mg</td>
</tr>
<tr>
<td></td>
<td>7 X 1000 (per week) =</td>
<td></td>
</tr>
<tr>
<td>Absorption</td>
<td>60%</td>
<td>4200 mg</td>
</tr>
<tr>
<td></td>
<td>7000 X 60% =</td>
<td></td>
</tr>
<tr>
<td>Dialysis</td>
<td>800 mg</td>
<td>4800 mg</td>
</tr>
<tr>
<td></td>
<td>6 X 800 (per week) =</td>
<td></td>
</tr>
<tr>
<td>Balance</td>
<td>4200 – 4800 =</td>
<td>- 600 mg</td>
</tr>
</tbody>
</table>

Dialysis: 60%
7000 X 60% = 4200 mg

Absorption: 60%
7000 X 60% = 4200 mg

Diet: 1000 mg/day
7 X 1000 (per week) = 7000 mg

Therapeutic Interventions for Managing Secondary HPT

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phosphate Binders</td>
<td>Ca</td>
</tr>
<tr>
<td>(Ca-based)</td>
<td>PO₄</td>
</tr>
<tr>
<td>PTH</td>
<td>↓</td>
</tr>
</tbody>
</table>


Phosphate Binders

**Aluminum-based**
- Aluminum hydroxide
- Aluminum carbonate

**Calcium-based**
- Calcium carbonate
  - Many OTC brands available
  - Frequently used
- Calcium acetate
  - PhosLo®

**Magnesium-based**
- Rarely used, limitations

**Aluminum- and calcium-free**
- Sevelamer hydrochloride
- Renagel®

**Magnesium- and calcium-free**
- Lanthanum carbonate
  - Fosrenol®
  - Renvela®
Aluminum-based Phosphate Binders

- **Benefit**
  - Effective

- **Limitations:** Toxic effect
  - Severe bone disease
  - Dementia
  - Muscle weakness
  - Anemia
  - Should be avoided

Rare Use of Aluminum

- Rarely used when refractory to other agents
  - Phosphorus > 7 mg/dL
  - Ca x P > 55

- Prior to using aluminum
  - Serum aluminum level < 20 mcg/L

- Aluminum - takes days to weeks to show effect
  - Should not be used for more than 30 days

Aluminum Drug Interactions

- Citrate increases aluminum absorption
- Aluminum is a component of other medications
  - Maalox® – Magnesium Aluminum Hydroxide
  - Sucralfate® – Sucrose Aluminum Phosphate
  - Amhoge®
**Calcium-based Phosphate Binders**

**Calcium Carbonate**
- **Benefits**
  - Effective phosphate binder
  - Ca supplement
- **Limitations or side effects**
  - Limited long-term data
  - Hypercalcemia
  - Associated with soft tissue calcification
  - GI side effects

**Calcium Acetate**
- **Benefits**
  - Effective phosphate binder
- **Limitations or side effects**
  - Hypercalcemia
  - GI side effects

**KDOQI: Use of Calcium-containing Phosphate Binders**
- Do not use Calcium-based binders if:
  - Hypercalcemia (>10.2 mg/dL)
  - PTH <150 pg/mL
  - Severe extraskeletal calcification

**Calcium Content of Common Calcium-based Binders or Supplements**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Brand Name</th>
<th>Compound Content (mg)</th>
<th>% Calcium</th>
<th>Elemental Calcium (mg)</th>
<th>No. of Tablets/Equal to 1 mg Elemental Calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium Acetate</td>
<td>PhosLo**</td>
<td>607</td>
<td>25%</td>
<td>157</td>
<td>9</td>
</tr>
<tr>
<td>Calcium Carbonate</td>
<td>Caltrate** (Bristol-Myers Squibb)</td>
<td>500</td>
<td>40%</td>
<td>200</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td>TUMS C Item (extra strength)</td>
<td>750</td>
<td>40%</td>
<td>300</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>TUMS Ultra**</td>
<td>1,500</td>
<td>40%</td>
<td>600</td>
<td>3.75</td>
</tr>
<tr>
<td></td>
<td>LanCot**</td>
<td>1,250</td>
<td>40%</td>
<td>500</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Calcitran®</td>
<td>1,250</td>
<td>40%</td>
<td>500</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>CalciPure®</td>
<td>1,250</td>
<td>40%</td>
<td>500</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Calci-Soft®</td>
<td>1,500</td>
<td>40%</td>
<td>600</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>Caltrate 300™</td>
<td>1,500</td>
<td>40%</td>
<td>600</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>NaphosCalc**</td>
<td>1,500</td>
<td>40%</td>
<td>600</td>
<td>2.5</td>
</tr>
</tbody>
</table>

**Calcium Gluconate**

**Magnesium Carbonate**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Brand Name</th>
<th>Compound Content (mg)</th>
<th>% Magnesium</th>
<th>Elemental Magnesium (mg)</th>
<th>No. of Tablets/Equal to 1 mg Elemental Magnesium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium Gluconate</td>
<td>Glucemate** (Purdue Frederick)</td>
<td>200</td>
<td>Magnesium carbonate</td>
<td>57 mg</td>
<td>13</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Magnesium**</td>
<td>400 Calcium</td>
<td>Magnesium</td>
<td>155 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>500 Magnesium</td>
<td>Magnesium</td>
<td>50 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>300 Magnesium</td>
<td>Magnesium</td>
<td>30 mg</td>
<td></td>
</tr>
</tbody>
</table>

**NKF KDOQI Clinical Practice Guideline 2009**

---

**Calcium Carbonate**
- Effective phosphate binder
- Ca supplement

**Calcium Acetate**
- Effective phosphate binder

**Limitations or side effects**
- Hypercalcemia
- GI side effects

**Do not use Calcium-based binders if:**
- Hypercalcemia (>10.2 mg/dL)
- PTH <150 pg/mL
- Severe extraskeletal calcification

**KDOQI: Use of Calcium-containing Phosphate Binders**

**Calcium Content of Common Calcium-based Binders or Supplements**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Brand Name</th>
<th>Compound Content (mg)</th>
<th>% Calcium</th>
<th>Elemental Calcium (mg)</th>
<th>No. of Tablets/Equal to 1 mg Elemental Calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium Acetate</td>
<td>PhosLo**</td>
<td>607</td>
<td>25%</td>
<td>157</td>
<td>9</td>
</tr>
<tr>
<td>Calcium Carbonate</td>
<td>Caltrate** (Bristol-Myers Squibb)</td>
<td>500</td>
<td>40%</td>
<td>200</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td>TUMS C Item (extra strength)</td>
<td>750</td>
<td>40%</td>
<td>300</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>TUMS Ultra**</td>
<td>1,500</td>
<td>40%</td>
<td>600</td>
<td>3.75</td>
</tr>
<tr>
<td></td>
<td>LanCot**</td>
<td>1,250</td>
<td>40%</td>
<td>500</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Calcitran®</td>
<td>1,250</td>
<td>40%</td>
<td>500</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>CalciPure®</td>
<td>1,250</td>
<td>40%</td>
<td>500</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Calci-Soft®</td>
<td>1,500</td>
<td>40%</td>
<td>600</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>Caltrate 300™</td>
<td>1,500</td>
<td>40%</td>
<td>600</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td>NaphosCalc**</td>
<td>1,500</td>
<td>40%</td>
<td>600</td>
<td>2.5</td>
</tr>
</tbody>
</table>

**Calcium Gluconate**
- Not Recommended

**Magnesium Carbonate**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Brand Name</th>
<th>Compound Content (mg)</th>
<th>% Magnesium</th>
<th>Elemental Magnesium (mg)</th>
<th>No. of Tablets/Equal to 1 mg Elemental Magnesium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium Gluconate</td>
<td>Glucemate** (Purdue Frederick)</td>
<td>200</td>
<td>Magnesium carbonate</td>
<td>57 mg</td>
<td>13</td>
</tr>
<tr>
<td>Magnesium</td>
<td>Magnesium**</td>
<td>400 Calcium</td>
<td>Magnesium</td>
<td>155 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>500 Magnesium</td>
<td>Magnesium</td>
<td>50 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>300 Magnesium</td>
<td>Magnesium</td>
<td>30 mg</td>
<td></td>
</tr>
</tbody>
</table>
Phosphate Binders and Mortality

Phosphate Binders and Calcification

Sevelamer Hydrochloride (Renagel®)
Sevelamer Carbonate (Renvela®)

- Patients not taking a phosphate binder: 800-1600 mg 3 times/day with meals
- The initial dose may be based on serum phosphorous levels
  - >5.5 mg/dL to <7.5 mg/dL: 800 mg 3 times/day
  - ≥7.5 mg/dL to <9.0 mg/dL: 1200-1600 mg 3 times/day
  - ≥9.0 mg/dL: 1600 mg 3 times/day
- Switching from Renagel & Renvela
  - Same dose (on a mg per mg basis) may be utilized
- Switching from PhosLo to Renagel or Renvela
  - 667 mg of PhosLo is equivalent to 800 mg sevelamer
Sevelamer: Benefits & Caveats

**Benefits**
- Works as nonabsorbable polymer
- Effective as monotherapy
- Minimal drug interaction, except ciprofloxacin
- Does not cause hypercalcemia/calcifications
- Effective LDL lowering effects

**Caveats**
- Bloating/Nausea/Vomiting
- Expands upon contact with water
- Avoid in intestinal obstruction
- Can not crush or give via feeding tube
- Metabolic acidosis seen with hydrochloride form not with carbonate form
- Cost

Lanthanum Carbonate (Fosrenol®)

**Mechanism**
- Absorbed in upper GI tract dissociates into lanthanum ion ($\text{La}^{3+}$), binds to dietary phosphate
- Effective as monotherapy
- No drug interactions
- No significant side effects
- Cost is a big issue

Use of Phosphate Binders

<table>
<thead>
<tr>
<th></th>
<th>1st line</th>
<th>2nd line</th>
<th>3rd line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 3/4</td>
<td>Dietary P restriction</td>
<td>Ca-based binder</td>
<td></td>
</tr>
<tr>
<td>Stage 5</td>
<td>Dietary P restriction, Ca-based or other binder</td>
<td>Ca-based and other binder</td>
<td>Al(OH) up to 4 sets</td>
</tr>
</tbody>
</table>

- Ca-based binder should not be used if patient has hypercalcemia or PTH < 150 pg/mL.
- Non-Ca-based binder preferred if vascular or soft-tissue calcification is appreciable

NKF K/DOQI Clinical Practice Guidelines 2009
Phosphate Binders: Summary

<table>
<thead>
<tr>
<th>Binder</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum-containing</td>
<td>Effective</td>
<td>Tissue accumulation; Bone disease, encephalopathy, anemia</td>
</tr>
<tr>
<td>Calcium-containing</td>
<td>Effective; Widely used</td>
<td>Hyper-Ca, calcification risk; High pill burden</td>
</tr>
<tr>
<td>Sevelamer</td>
<td>Less vascular calcification than Ca-containing binders; lower mortality? Reduction of LDL</td>
<td>High pill burden (moderate potency); Cost</td>
</tr>
<tr>
<td>Lanthanum carbonate</td>
<td>Good potency; Minimal absorption; Not hyper-calcemic; Low pill burden</td>
<td>Cost</td>
</tr>
</tbody>
</table>

Physiology of Calcium and Phosphorus Metabolism

Roles of vitamin D and parathyroid hormone in regulating serum calcium levels

Secondary HPT Pathophysiology: Recap

- Chronic kidney disease disrupts calcium homeostasis
  - High PTH ➔ Leads to bone resorption
  - Reduced intestinal calcium absorption
  - Low serum calcium at low GFR
  - High serum phosphorus at low GFR
  - Low calcitriol
- Excess PTH synthesis and secretion
  - Hyperplasia and parathyroid gland enlargement contribute to elevated serum PTH
Therapeutic Interventions for Managing Secondary HPT

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D Analog</td>
<td>PTH ↓</td>
</tr>
<tr>
<td></td>
<td>Ca ↑</td>
</tr>
<tr>
<td></td>
<td>PO₄³⁻↑</td>
</tr>
</tbody>
</table>


Initial Dosing of Oral Vitamin D Stage 3 & 4 Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dose</th>
<th>Titration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcitriol (Rocaltrol®)</td>
<td>0.25 mcg/d or QOD</td>
<td>↑ Q4 – 8 week</td>
</tr>
<tr>
<td>Doxercalciferol (Hectorol®)</td>
<td>1 mcg/d</td>
<td>↑ By 0.5 mcg Q2 weeks</td>
</tr>
<tr>
<td>Paracalcitol (Zemplar®)</td>
<td>PTH ≤500 – 1 mcg/d or 2 mcg QOD; PTH &gt; 500 – 2 mcg/d or 4 mcg QOD</td>
<td>↑ Q2 – 4 weeks</td>
</tr>
</tbody>
</table>

Vitamin D Analogs

- Calcitriol (Calcijex, Rocaltrol)
  - Similar to endogenous form
  - Higher affinity to vitamin D receptors in intestines and PTH gland
  - Higher incidence of hypercalcemia/hyperphosphatemia
  - Least expensive
- Doxercalciferol (Hectorol®)
  - Prodrug: requires functioning liver for efficacy
- Paracalcitol (Zemplar®)
Initial Dosing of Vitamin D
Stage 5 Chronic Kidney Disease

<table>
<thead>
<tr>
<th>PTH</th>
<th>Ca</th>
<th>P</th>
<th>Ca x P</th>
<th>Calc (mcg)</th>
<th>Para (mcg)</th>
<th>Dox (mcg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>IV: 0.5 - 1.5</td>
<td>PO: 0.5 - 1.5</td>
<td>IV: 2</td>
</tr>
<tr>
<td>&lt;500</td>
<td>&lt;9.5</td>
<td>&lt;55</td>
<td>&lt;55</td>
<td>IV: 6 - 10</td>
<td>PO: NONE</td>
<td>IV: 2 - 4</td>
</tr>
<tr>
<td>&gt;500</td>
<td>&lt;9.5</td>
<td>&lt;55</td>
<td>&lt;55</td>
<td>IV: 10 - 15</td>
<td>PO: NONE</td>
<td>IV: 4 - 8</td>
</tr>
</tbody>
</table>

Survival by Type of Vitamin D Analog

Vitamin D Use Is Associated With Decreased Mortality in Incident HD Patients
Interplay Between Vitamin D, Calcium & Phosphate Therapy

- Serum Ca > 10.2
  - Stop all D, minimize Ca load
- Ca = 9.5 - 10.2
  - Change to non Ca-containing binder
- Ca < 9.5
  - Continue D or modify with P algorithm

Interplay Between Vitamin D, Calcium & Phosphate Therapy

- P > 6.0
  - Stop vitamin D
- P = 5.5 – 6.0
  - Increase binders, decrease Vitamin D
  - Restrict Ca-based binder to no more than 1500 mg elemental calcium
- P < 5.5
  - Continue or modify using Ca or PTH algorithm

KDOQI™ Biochemical Targets for Stage 5 CKD

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Target Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum PTH</td>
<td>150 – 300 pg/mL</td>
</tr>
<tr>
<td>Serum Ca (albumin-corrected)</td>
<td>8.4 – 9.5 mg/dL</td>
</tr>
<tr>
<td>Serum P</td>
<td>3.5 – 5.5 mg/dL</td>
</tr>
<tr>
<td>Ca x P product</td>
<td>&lt; 55 mg²/dL²</td>
</tr>
</tbody>
</table>
Cinaclacet: Mechanism of Action

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcimimetic</td>
<td>PTH ↓</td>
</tr>
<tr>
<td>Cinacalcet (Sensipar®)</td>
<td>Ca ↓</td>
</tr>
<tr>
<td></td>
<td>PO₄↓</td>
</tr>
</tbody>
</table>


Cinaclacet Dosing

- Initial dose: 30 mg PO once daily
  - Titrated by 30 mg every 2 – 4 weeks
  - Max: 180 mg per day
- Adverse events
  - Nausea/vomiting
    - Generally self-limiting
  - Hypocalcemia
    - Most concerning

Cinaclacet Monitoring Parameters

- Initiated if corrected calcium < 8.4 mg/dL
  - Calcium & Phosphate obtained in 1 week & 1 month after initiation or any dose change
  - PTH obtained between 1 week – 1 month after initiation or any dose change
- Used concomitantly with vitamin D or phosphate binders
  - May assist with offsetting hypercalcemia induced by calcium based binders or vitamin D analogs
- Discontinue if PTH is below target range
Cinacalcet Drug interactions

- Cinacalcet inhibits CYP450: 2D6 & 3A4
  - Codeine → prodrg converted to morphine via 2D6
  - Tramadol → metabolized by 2D6
  - Beta-blockers: ex. Nebivolol® → new beta-blocker metabolized by 2D6
  - Warfarin → R isomer less potent metabolized by 3A4

Therapeutic Interventions for Managing Secondary HPT

- Calcimimetics, Vitamin D → PTH
- Diet/nutrition, Vitamin D → Ca
- Diet/nutrition, Phosphate Binders, Vitamin D → PO₄

Adapted from Goodman WG. Nephrol Dial Transplant. 2003;18(suppl 3):i3-i8.

Patient Case

- 53-year-old male with history of stage 5 CKD secondary to renal transplant rejection
- Recently started on hemodialysis
- History of CVD, s/p CABG x 3 in 02/07
- History HTN; history basal cell carcinoma
- Social history: works as car mechanic; smokes 2 PPD, no history of alcohol; married 21 years; 1 daughter, age 19
Patient Case

- Presents with mild itching, bone pain
- No history of fractures
- Medications:
  - Calcium acetate: 667 mg 3 tab tid
  - B-complex with C: 1 tab qd
  - Atorvastatin: 20 mg qd
  - Metoprolol: 50 mg bid
  - Prednisone: 2.5 mg qd
- Laboratory values:
  - Phosphorus: 8.0 mg/dl
  - Corrected calcium: 8.3 mg/dl
  - Intact PTH: 670 pg/ml
  - Ca x P: 66.4

...Cont'd

Nutrition Guidelines

- Limit dietary phosphorus to 800-1000 mg/d with consideration for protein needs, ie, as low as possible while allowing for a recommended level of protein intake
- Limit elemental calcium from calcium-based binders to ≤ 1500 mg/d
- Limit total (dietary and medication) elemental calcium to ≤ 2000 mg/d
- Avoid calcium fortified foods as directed
- Moderate application of cardiovascular dietary recommendations, not to the detriment of nutrition status
- Counsel on smoking cessation - minimize CVD risk


Patient Case Review

- Patient started on sevelamer HCl 800 mg 2 tablets TID with meals, Ca acetate discontinued to reduce vascular calcification risk
- Repeat labs after 2 weeks:
  - Phosphorus: 6.5 mg/dl
  - Corrected calcium: 8.3 mg/dl
  - Ca x P: 54
- Diet reviewed; sevelamer increased to 3 tablets with meals, 2 tablets with snacks
Patient Case Review

- At 1 month, labs are checked
  - Phosphorus: 5.5 mg/dL
  - Corrected calcium: 8.3 mg/dL
  - Ca x P: 46
  - Intact PTH: 601 pg/mL
  - 25-hydroxy vitamin D serum level: 40 ng/mL
- Started on Vitamin D
  - Calcitriol: 0.25 mcg PO Daily

...Cont'd

Patient Case Review

- Laboratory data in one month:
  - Phosphorus: 6.1 mg/dl
  - Calcium: 9.3 mg/dl
  - Ca x P product: 57
  - Intact PTH: 489 pg/ml
- Patient started on cinacalcet HCl 30 mg qd

...Cont'd

Patient Case Review

- Lab values checked at 1 week:
  - Phosphorus: 5.4 mg/dL
  - Corrected calcium: 8.7 mg/dL
- Patient complains of mild nausea
- Advised to take cinacalcet with evening meal
- No other changes made at this time

...Cont'd
Patient Case Review

- Labs rechecked at 1 month
  - Phosphorus: 5.4 mg/dL
  - Corrected calcium: 8.7 mg/dL
  - Intact PTH: 290 pg/ml
  - Ca x P product: 47
- Nausea resolved
- No further changes warranted at present

Developing a Treatment Algorithm

- Promote patient safety and incorporate strategies for the fewest side effects
- Be consistent with current, valid research and update regularly as new information is available
- Reflect team consensus and consider facility needs or limitations
- Provide a schedule for changes
  - Dose, meds, route of administration
- Provide logical, easy steps

- Allow for therapy response time before making additional changes
- Minimize paperwork
- Include mechanism to inform patient and team of progress
- Define limits and provide mechanism to return management to MD if treatment outside parameters is needed
- Identify outcome measures and provide tracking mechanisms
Therapeutic Options for Secondary HPT: Conclusion

- New phosphate binders offer options for phosphorus reduction without increasing serum calcium
- Vitamin D analogs lower PTH and increase bone mineralization, but also raise calcium and phosphorus
- Cinacalcet can be used to lower PTH despite elevations in calcium and/or phosphorus
- Dialysis is a critical tool for managing ESRD
- Parathyroidectomy can be useful for lowering PTH when pharmacologic intervention fails