DENOSUMAB INDUCED PARATHYROID HORMONE RESISTANCE CAUSING SEVERE HYPOCALCEMIA

Mahmoud Alsayed M.D.
Endocrinology Fellow PGY5
University of Arizona COM-Phoenix
Banner-University Medical Center
Phoenix VA Medical Center
Calcium is essential for:

- Vascular contraction and vasodilation
- Muscle function
- Nerve transmission
- Intracellular signaling and hormonal secretion

Ionized calcium concentration in plasma is under strict hormonal control and does not fluctuate with changes in dietary intake.
Background:

- Parathyroid hormone and Calcitriol mediate calcium balance primarily by:
  - Intestinal absorption
  - Bone formation and resorption
  - Urinary excretion
Background:

Sascha Kopic, and John P. Geibel Physiol Rev 2013;93:189-268
Case Presentation:

History of Presenting Illness:
- 88 year-old man was admitted to the ICU for sepsis with GI source.
- On hospitalization Day 11, Endocrinology team was consulted for hypocalcemia refractory to treatment

Past Medical History:
- Hyperthyroidism
- Osteoporosis
- CKD III
- History of prostate cancer, status post radiation (in 2000)
- History of small bowel obstruction, status post exploratory laparotomy
- Atrial fibrillation
- Sick sinus syndrome status post pacemaker placement
- Hypertension
- Parkinson's disease
Case Presentation:

Outpatient Medication List:

- Denosumab 60 mg subcutaneous (last dose 10 days before admission)
- Methimazole 5 mg daily
- Vitamin D2
- Carbidopa/levodopa
- Amlodipine
- Lisinopril
- Metoprolol
- Aspirin
- Dutasteride
- Quetiapine
- Sodium bicarbonate
Case Presentation:

Course of hospitalization was complicated with:

• GI bleed:
  • NPO except medication
  • Blood transfusion X6 units of pRBCs
  • Negative work up

• Acute respiratory failure:
  • Intubation and mechanical ventilation for 2 days

• Severe symptomatic hypocalcemia
  • Total of 45 gm of intravenous Calcium in 10 days
  • Doxercalciferol IV 0.5 mcg, 4 doses
## Case Presentation:

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 10</th>
<th>Day 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>5.7</td>
<td>6.5</td>
<td>6.9</td>
</tr>
<tr>
<td>PTH</td>
<td></td>
<td>706</td>
<td></td>
<td>151</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>1.9</td>
<td>1.9</td>
<td>1.5</td>
<td>1.5</td>
<td>1.8</td>
</tr>
<tr>
<td>Mg</td>
<td>1.6</td>
<td>1.8</td>
<td>2.5</td>
<td>2.5</td>
<td>1.9</td>
</tr>
<tr>
<td>Vitamin D, 25(OH)</td>
<td></td>
<td>23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ionized Calcium</td>
<td>2.48</td>
<td>3.09</td>
<td>3.53</td>
<td>4.37</td>
<td>4.57</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>2.5</td>
<td></td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D, 1, 25 (OH)2</td>
<td></td>
<td></td>
<td></td>
<td>99</td>
<td>18-72 pg/mL</td>
</tr>
<tr>
<td>Calcium 24 HR Urine</td>
<td></td>
<td>11</td>
<td>145</td>
<td></td>
<td>55-300 mg/24 h</td>
</tr>
<tr>
<td>Phosphorus 24 Hr Urine</td>
<td></td>
<td></td>
<td></td>
<td>9.3</td>
<td>360-1600 mg/24 h</td>
</tr>
</tbody>
</table>
Case Presentation:

**Labs on day 14**

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-Telopeptide (NTX)</td>
<td>16</td>
<td>30-59 years: 9-60 nmol BCE/nmol creat</td>
</tr>
<tr>
<td>C-Telopeptide (CTX)</td>
<td>852</td>
<td>50-68 years: 87-345, pg/ml</td>
</tr>
<tr>
<td>Procollagen I Propeptide (P1NP)</td>
<td>65</td>
<td>25-70 years: 15–80 mcg/L</td>
</tr>
<tr>
<td>Alkaline Phos. Bone specific</td>
<td>13.3</td>
<td>50-68 years: 7.6-14.9 mcg/L</td>
</tr>
</tbody>
</table>
Discussion

Denosumab induced hypocalcemia

✓ Mechanism
✓ Risk factors
✓ Who to monitor and when
✓ How to avoid
Mechanism of Denosumab Induced Hypocalcemia

- RANKL
- RANK
- OPG
- denosumab

Growth Factors
Hormones
Cytokines

CFU-M
Pre-Fusion Osteoclast
Multinucleated Osteoclast
Osteoclast

RANKL

Osteoblast Lineage
Bone

CFU-M = colony forming unit macrophage
Denosumab Induced Hypocalcemia

- Predisposing factors:
  - History of hypoparathyroidism
  - Thyroid or parathyroid surgery
  - Malabsorption
  - Excision of small intestine
  - Severe renal impairment [creatinine clearance < 30 mL/min]
  - Receiving dialysis

Denosumab Induced Hypocalcemia

- The nadir in Calcium level occurs at approximately day 10 after Denosumab dosing
- Pre-existing hypocalcemia must be corrected
- Adequately supplement all patients with calcium and vitamin D
- Monitoring (Ca, Phos, Mg) within 14 days of the injection is highly recommended for patients with predisposing factors

Acknowledgments

• Faculty
  • Dr. Allison Peckumn
  • Dr. Jerome Targovnik

• Colleagues
  • Dr. Jeans Choi