2 Year old Girl with Severe Hypercalcemia

March 7, 2013
Matt Wise, MD
All ages
2y3m caucasian girl presents to OSH ER with 1 day of fever to 102, vomiting, increased tiredness
- Several weeks of excess thirst, urination
- 103.4, HR 158, 104/68
- Looks well, ER physician unconcerned; parent requests blood work noting prior problem with vitamin D deficiency
- Ca 16.2 mg/dL (2-12y: 8.8-10.8), BUN 32/Cr 1.4
- 20mL/kg NS bolus and transfer to Comer
Further History

- Chronic constipation since age 1
- At 2yr well child check: vitamin D assessed to be 20 ng/mL
- Advised to start supplement 2000 IU/d
- Parents obtain D3 oral solution 2000 IU/gtt
- Child receives 1mL = 30gtt = 60,000 IU/d x3mo = 5.4 million IUs!
- Diet: up to 1L of rice milk/day, 3 yogurts/day, frequent cheese slices
PMH
- Full term infant, uncomplicated pregnancy
- Breastfed; jaundice
- Chronic constipation
- Vit D def

FH
- Mother/father healthy
- high calcium
- kidney stones
- parathyroid, pancreas, adrenal tumors

SH
- Lives with both parents

Meds
- D3 60,000 IU qd x3mo
- MVI with 200 IU D
- Probiotic
- Miralax prn
Physical Exam

Height 86.3cm (35%)  Weight 13.2kg (67%)  T 35.9  HR 145  RR 35  BP 138/70
Constitutional: Active, alert
HENT: Mouth/Throat: mucous membranes moist.
Eyes: EOM are normal. Pupils are equal, round, and reactive to light.
Cardiovascular: Normal rate and regular rhythm. No murmur heard.
Pulmonary/Chest: Effort normal and breath sounds normal.
Abdominal: Soft. No tenderness or hepatosplenomegaly
Genitourinary: prepubertal female external genitalia
Musculoskeletal: No bony deformities, normal spine alignment
Neurological: CN 2-12 intact, She displays normal reflexes.
Psych: irritable, consoles with parents
Skin: no rashes or birthmarks
Differential Dx

**PTH dependent**
- Primary hyperparathyroidism
- Neonatal severe hyperparathyroidism
- Neonatal hyperparathyroidism
- MENI, IIA

**PTH independent**
- FHH
- Vit D intoxication
- granulomatous disease
- Childhood malignancy
- Immobilization
- Lightwood syndrome
- Williams syndrome
- Jansen’s metaphyseal chondrodysplasia
Further Evaluation

- Ca 13.9 (13.3), Phos 6.2, Mg 3.1, alk phos 175
- Ionized Ca 7.6 (4.6-5.4), Alb 4.8, Cre 1.4
- Lipase 14
- EKG: QTc 426 (normal <440 in children)
- PTH 16 pg/mL (15-75)
- 25-D >100 ng/mL --- 690 ng/mL
- 1,25-D “interfering substances”
  repeated: 61 pg/mL (24-86)
Renal US

Bilateral nephrocalcinosis
Enlarged kidneys
Bilateral hydronephrosis
Initial Management

- Hydration (NS at 2x maintenance)
- Calcitonin (~ 4U/kg/d divided bid)
- Prednisolone (~ 2mg/kg/d divided bid)
- Nephrology and Nutrition consults (low Ca diet)

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Narrative Review: Furosemide for Hypercalcemia: An Unproven yet Common Practice

Susan B. LeGrand, MD; Dona Leskuski, DO; and Ivan Zama, MD

Although primary hyperparathyroidism is the most common cause of hypercalcemia, cancer is the most common cause requiring inpatient intervention. An estimated 10% to 20% of all patients with cancer have hypercalcemia at some point in their disease trajectory, particularly in advanced disease. Aggressive saline hydration and varying doses of furosemide continue to be the standard of care for emergency management. However, a review of the evidence for the use of furosemide in the medical management of hypercalcemia yields only case reports published before the introduction of bisphosphonates, in contrast to multiple randomized, controlled trials supporting the use of bisphosphonates. The use of furosemide in the management of hypercalcemia should no longer be recommended.

For author affiliations, see end of text.
Hospital and Post-Discharge Course

- IV hydration: 2x maintenance → 1x maintenance
- Calcitonin: 4.5U/kg/d
- Prednisolone: 2mg/kg/d
- Alendronate: 5mg po x2
A curveball!

- On the morning of our planned discharge, PTHrp returned as 6.5 pmol/L (<2.0)!!
- CBC: **WBC 46.6!** (prior on admission WBC 11)  
  diff: normal
- Was felt related to glucocorticoids
- Repeat 2 days after discharge: WBC 24
Clinical Questions

- What is the mechanism of hypercalcemia in vitamin D intoxication?
- What is the experience with bisphosphonates in treating hypercalcemia from vit D toxicity?
Vitamin D Intoxication

- AAP 2008: 200 IU-400 IU/d infants + children
- IOM 2011: 200 IU-400 IU/d 0-12mo
  200 IU-600 IU/d 1-8 years
- High concentration preps increasingly available
Vitamin D Supplement Products: Medication Use Error

Audience: Pediatrics, Family Practice, Consumer

[Posted 06/15/2010]

ISSUE: Some liquid Vitamin D supplement products are sold with droppers that could allow parents to accidentally give harmful amounts of Vitamin D to their infant. Excessive amounts of Vitamin D can be harmful to infants, and may be characterized by nausea and vomiting, loss of appetite, excessive thirst, frequent urination, constipation, abdominal pain, muscle weakness, muscle and joint aches, confusion, and fatigue, as well as more serious consequences like kidney damage.

BACKGROUND: The American Academy of Pediatrics has recommended a dose of 400 International Units (IU) of Vitamin D Supplement per day to breast-fed and partially breast-fed infants (AAP Pediatric Nutrition Handbook, 6th edition, p.466).

RECOMMENDATION: The easiest way to insure that an infant will not get more than the recommended dose is to use a product supplied with a dropper that will give no more than 400 IU per dose. If a caregiver cannot clearly determine the dose of Vitamin D that should be given to an infant or has any other questions, FDA recommends consulting with a healthcare provider before giving any of these products to an infant.

Healthcare professionals and patients are encouraged to report adverse events or side effects related to the use of these products to the FDA’s MedWatch Safety Information and Adverse Event Reporting Program:

- Online: www.fda.gov/medwatch/report.htm
- Phone: 1-800-332-1088
- Mail: return the postage-paid FDA form 3500, which may be downloaded from the MedWatch "Download Forms" page, to address on the pre-addressed form
- Fax: 1-800-FDA-0178

[06/15/2010 - Note to Correspondents - FDA]
[06/15/2010 - Consumer Update - FDA]
Vitamin D Intoxication

Vitamin D intoxication causes hypercalcaemia by increased bone resorption which responds to pamidronate

Clinical Endocrinology (1995) 43, 531–536
P. L. Selby, M. Davies, J. S. Marks* and E. B. Mawer

- Components of hypercalcemia studied in patients with vitamin D toxicity
  - Increased renal tubular reabsorption
  - Reduced GFR
  - Increased “throughput”: GI absorption/bone reabsorption
- 1,25 D known to have bone resorbing action
- Large concentrations of 25-D able to stimulate bone resorption independently
Bisphosphonates for HyperCa in Children

- Adverse effects:
  - **ONJ**: not a single case report in children
  - **Growth impairment**: unproven!
    - benefit on growth seen in OI (through 18mo)
    - use in vit D intox: 1 case series and many reports (pamidronate and alendronate)
  - Esophagitis
  - Flu-like symptoms
  - Hypocalcemia
Pamidronate for HyperCa in Children

2007: 16mo old boy with overdose of vit D (quantity unclear)
White arrow: hydration, lasix, glucocorticoids
Black arrow: pamidronate 1mg/kg IVx1

Graph showing serum calcium levels over 72 days.
Alendronate for HyperCa in Children

- 3mo old infant 1.2 million IU of vit D

TABLE 1. Laboratory Values and Treatment During Admission and Follow-up

<table>
<thead>
<tr>
<th>Time</th>
<th>Calcium (mg/dL)</th>
<th>Parathyroid Hormone (pg/mL)</th>
<th>Urinary Calcium/Creatinine</th>
<th>P (mg/dL)</th>
<th>Alkaline Phosphatase (U/L)</th>
<th>Vitamin D (ng/mL)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>18.5</td>
<td>&lt;1.0</td>
<td>1.15</td>
<td>3.2</td>
<td>492</td>
<td>360</td>
<td>Hydration, diuretic</td>
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<tr>
<td>Day 2</td>
<td>17.6</td>
<td></td>
<td>2.22</td>
<td>3.5</td>
<td></td>
<td></td>
<td>Alendronate, 5 mg</td>
</tr>
<tr>
<td>Day 3</td>
<td>16.7</td>
<td></td>
<td></td>
<td>2.7</td>
<td></td>
<td></td>
<td>Alendronate, 10 mg</td>
</tr>
<tr>
<td>Day 4</td>
<td>13.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Alendronate, 10 mg</td>
</tr>
<tr>
<td>Day 6</td>
<td>12.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Alendronate, 5 mg, discharge</td>
</tr>
<tr>
<td>Day 18</td>
<td>9.9</td>
<td>9.1</td>
<td></td>
<td>3.5</td>
<td></td>
<td>439</td>
<td>Alendronate discontinued</td>
</tr>
<tr>
<td>2 mo</td>
<td>10.3</td>
<td></td>
<td></td>
<td>0.59</td>
<td>4.1</td>
<td>750</td>
<td>No treatment</td>
</tr>
<tr>
<td>4 mo</td>
<td>10.3</td>
<td></td>
<td>0.08</td>
<td>4.1</td>
<td>6.6</td>
<td>750</td>
<td>No treatment</td>
</tr>
<tr>
<td>6 mo</td>
<td>10.1</td>
<td></td>
<td></td>
<td></td>
<td>6.4</td>
<td>368</td>
<td>No treatment</td>
</tr>
<tr>
<td>Normal range</td>
<td>8.9–10.1</td>
<td>8–74</td>
<td>&lt;0.2</td>
<td>3.6–5.5</td>
<td>250–850</td>
<td>10–40</td>
<td></td>
</tr>
</tbody>
</table>

f//u at 18 month of age: normal growth at same percentiles

Bereket Pediatrics 2003
Alendronate for HyperCa in Children

4 children treated with alendronate: 5 year f/u with normal growth

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Total vitamin D dose received (IU)</th>
<th>Ca (mmol/L) (admission/discharge) N = 2.2–2.7</th>
<th>25-OH-vitamin D (µg/L) N = 20–120</th>
<th>iPTh (pmol/L) N = 1.3–9.3</th>
<th>Duration of steroid treatment (Days)</th>
<th>Time to normocalcemia after single dose of alendronate* (Days)</th>
<th>Day at level of Ca ≤ 2.7 mmol/L achieved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>7</td>
<td>600.000</td>
<td>3.9/2.62</td>
<td>350</td>
<td>0.52</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Case 2</td>
<td>7</td>
<td>600.000</td>
<td>4.77/2.7</td>
<td>430.12</td>
<td>0.10</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>Case 3</td>
<td>8</td>
<td>1,500.000</td>
<td>3.8/2.72</td>
<td>250</td>
<td>0.52</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Case 4</td>
<td>5</td>
<td>900.000</td>
<td>4.12/2.42</td>
<td>280</td>
<td>0.63</td>
<td>15</td>
<td>17</td>
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<tr>
<td>Case 5</td>
<td>10</td>
<td>1,800.000</td>
<td>3.8/2.2</td>
<td>572.5</td>
<td>0.63</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Case 6</td>
<td>11</td>
<td>264.000</td>
<td>4.25/2.55</td>
<td>204</td>
<td>0.63</td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>
Take Home Points

1) Vitamin D toxicity may be increasing in incidence due to recent recommendations and the availability of high concentration formulations.

2) Bisphosphonates have been shown to be safe, effective in the management of severe hypercalcemia related to vit D toxicity though long term effects in children are not well defined.
References

- Chatterjee M. Pamidronate treatment of hypercalcemia caused by vitamin D toxicity. JPEM 2007; 20:1241.
- Jones G. Pharmacokinetics of vitamin D toxicity. Am J Clin Nutr 2008;88(S):582S.
- Selby P. Vitamin D intoxication causes hypercalcemia by increased bone resorption which responds to pamidronate. Clinical Endocrinology 1995; 43:531.