Excessive accumulation of aluminum (Al) in the bones of patients on long term parenteral nutrition (PN): post-mortem analysis

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Introduction to Aluminum (Al)

- Al comprises 8% of Earth's crust
  - contaminates food, water, and extracted minerals

- Healthy adults ingest ~3-5 mg Al/day, but only absorb ~15 µg/day (gastrointestinal barrier)

- A small amount reaches blood, is bound by proteins, and is eventually excreted through the kidneys
Introduction to Aluminum (Al)

• Al toxicity can occur if:
  – renal excretion is impaired (uremic, dialysis patients)
  – gastrointestinal barrier is bypassed (parenteral nutrition)

• Al toxicity can occur in:
  – bones (osteomalacia, fractures)
  – brain (premature dementia, seizures, death)
Aluminum in PN Patients

• Al toxicity associated with PN use well known since the early 1980's (adults and infants)
  – Al accumulation at mineralization front in bone
  – Impaired bone – mineral uptake (calcium)
  – Reduced bone formation
  
  – Bone pain (long bones, weight-bearing joints)
  – Osteomalacia
History of Aluminum Contamination in PN Solutions

- 1970’s: Switch from casein/fibrin hydrolysates to crystalline amino acids
- 1986: FDA recommends elimination of Al from ingredients used in PN solutions
- 1991: "Safe" level of Al administration through PN is
  \[< 2 \, \mu g \, Al/kg \, body \, weight/day\]
- 2004: FDA regulations
  - LVPs contain \(< 25 \, \mu g/L\)
  - SVPs are labeled with maximum Al concentrations at expiration
  - 'Warnings' section for toxicity of Al \(> 5 \, \mu g/kg/day\)
Measuring Aluminum in Bone

- Vertebrae or long bone samples from 7 long term PN patients collected at autopsy
- Control samples ($n = 18$) obtained from hip or knee replacement patients

- At least 2 cm x 2 cm in size
- Placed in acid-washed/Al-free plastic containers
- Stored in a -70°C freezer until analysis

- Clinical patient information also collected
Bone Preparation

1. Clean with H$_2$O$_2$
2. De-fat with diethyl ether
3. Freeze-dry
4. Section with Diamond Disc saw
5. Digest with HNO$_3$ in microwave
Bone Analysis

Graphite Furnace Atomic Absorption Spectrometry

light energy + ground state Al atom → excited state Al atom
<table>
<thead>
<tr>
<th>Patient #</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis leading to SBS</td>
<td>Bowel Ischemia</td>
<td>Bowel Ischemia</td>
<td>Bowel Ischemia</td>
<td>Bowel Ischemia</td>
<td>Crohn's Disease</td>
<td>Crohn's Disease</td>
<td>Crohn's Disease</td>
</tr>
<tr>
<td>Remaining bowel</td>
<td>duodenum + ½ colon</td>
<td>80 cm jejunum + ¾ colon</td>
<td>80 cm jejunum + ½ colon</td>
<td>55 cm jejunum + ½ colon</td>
<td>110 cm jejunum, no colon</td>
<td>80 cm jejunum, no colon</td>
<td>80 cm jejunum, no colon</td>
</tr>
<tr>
<td>Years on PN</td>
<td>2</td>
<td>10</td>
<td>12</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>21</td>
</tr>
<tr>
<td>Other disorders</td>
<td>kidney failure, dialysis 18 mos.</td>
<td>recurrent catheter sepsis, osteomyelitis</td>
<td>chronic renal disease</td>
<td>HTN</td>
<td>kidney failure, dialysis 8 mos.</td>
<td>cirrhosis, HepC+</td>
<td></td>
</tr>
</tbody>
</table>

CHF = congestive heart failure; HepC+ = hepatitis C positive; HTN = hypertension

Howard et al., JPEN 2007; 31(5): 388-396
Bone Aluminum Results

Bone Al (µg/g)

Error bars = standard deviation

Ref pop

Controls (C) n = 18

# years on PN

†Reference population (Tang et al. 1999. Biol Trace Elem Res; 68, 267-279)
Bone Samples

PN patient samples

Control samples
Where do we go from here?
Continuing Problems

• Where is Al still present?
  – PN additives: multivitamins, trace elements, Ca, Mg, and phosphate salts, heparin, albumin
    • contamination of PN solutions with Al is variable and unpredictable
  – other sources of Al?

• How can we reduce Al exposure?
  – use plastic containers for PN ingredients
  – replace Al-rich components ($C_{12}H_{22}CaO_{14}$ with $CaCl_2$ salts, $K_3PO_4$ with $Na_3PO_4$ salts)
Where do we go from here?
Monitoring PN Patient Bone Health

• Predictors of excess bone Al accumulation?
  – urine, plasma, serum, blood Al content
  – serum Al – deferoxamine (Al chelator) infusion test
  – iron status – anemia may cause easier Al absorption

• \textit{In vivo} neutron activation analysis in hand bone

• Other trace elements in bone
Acknowledgements

The Oley Foundation

Creighton University Osteoporosis Research Center
• Robert R. Recker, M.D.

Clinical Trace Elements Laboratory (NYS DOH)
• Aubrey Galusha
• Michelle Morrissette