A Liquid Calcium+Vitamin D Supplement is Effective Prophylaxis Against Hypocalcemic Toxicity During Apheresis Platelet Donation

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Hypocalcemic ("Citrate") Toxicity in Apheresis Platelet Donors

- Most common adverse effect of platelet apheresis
- Citrated plasma returned to donor: ↓ plasma [Ca$^{2+}$]
- Oral CaCO$_3$ to alleviate symptoms
- Prophylactic oral CaCO$_3$ at start of collection
  - Modest protection of [Ca$^{2+}$] level
  - No overall impact on occurrence of symptoms
- Repeat prophylactic dosing? Another oral calcium salt?

Bolan CD et al. Transfusion 2003;43:1403-13
Bolan CD et al. Transfusion 2003;43:1414-22
“Effect of Oral Calcium Supplementation on Plasma [Ca$^{2+}$] and Hypocalcemic Toxicity During Platelet Donation”

- **Study approved by UMass Medical School IRB**
  - Cohort A: no prophylactic calcium
    - intervention with CaCO$_3$ for symptoms only
  - Cohort B: Prophylactic CaCO$_3$
    - TUMS® (GlaxoSmithKline, Brentford, Middlesex, UK)
    - 1000 mg per dose
  - Cohort C: Prophylactic Ca$_3$(C$_6$H$_5$O$_7$)$_2$/Ca$_3$(PO$_4$)$_2$, Vit D$_3$
    - Wellesse® Calcium & Vit D$_3$ Liquid (Botanical Labs, Ferndale, WA)
    - $\frac{2}{3}$ Ca$_3$(C$_6$H$_5$O$_7$)$_2$, $\frac{1}{3}$ Ca$_3$(PO$_4$)$_2$
    - 1000 mg Ca & 1000 IU Vit D$_3$ per dose

- **Platelets collected with Trima Accel®**
Experimental Protocol
(During Apheresis Platelet Collection)

**Outcome Measures:** Change in $[Ca^{2+}]$ from baseline. Symptoms of hypocalcemic toxicity.

**Hypocalcemic Toxicity:** At minimum, a persistent and uncomfortable metallic taste and/or acral or perioral paraesthesias.
Measurement of Plasma $[\text{Ca}^{2+}]$ by Fingerstick Blood Sample

- iSTAT® System point-of-care blood analyzer
  - CG8+ cartridge
  - 95 µL blood sample
- Unistick 3 Comfort Lancet
- Natelson heparinized blood collection tubes (0.2 mL)
[Ca$^{2+}$] Equivalent in Capillary (Fingerstick) Blood and Venous (Antecubital) Blood

*Mann-Whitney Rank Sum Test

$p=0.543$
Plasma Ionized Calcium During Apheresis Platelet Donation

**No Prophylactic Calcium**

CaCO$_3$

$\text{Ca}_3(\text{C}_6\text{H}_5\text{O}_7)_2/\text{Ca}_3(\text{PO}_4)_2$

Reference range: 4.5-5.3 mg/dL

- **Avg Start**
- **Avg Mid**
- **Avg End**

** Platelet Donor Management Strategy

- $p<0.05$
- $p<0.05$
- $p<0.05$
- $p<0.05$
- $p<0.05$
- $p<0.05$

**Values:**

- No Prophylactic Calcium: $-18.1 \pm 4.3\%$
- CaCO$_3$: $-19.6 \pm 3.9\%$
- $\text{Ca}_3(\text{C}_6\text{H}_5\text{O}_7)_2/\text{Ca}_3(\text{PO}_4)_2$: $-24.5 \pm 6.1\%$

- Reference range: 4.5-5.3 mg/dL
Lower Rate of Hypocalcemic Toxicity with Liquid Ca/Vit D Prophylaxis

<table>
<thead>
<tr>
<th>Cohort</th>
<th>n</th>
<th>Hypocalcemic Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>A</td>
<td>25</td>
<td>12 48%</td>
</tr>
<tr>
<td>No Prophylactic Calcium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>10</td>
<td>6 60%</td>
</tr>
<tr>
<td>CaCO₃ 1000 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>26</td>
<td>5 19%</td>
</tr>
<tr>
<td>Ca₃(C₆H₅O₇)₂ (67%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ca₃(PO₄)₂ (33%)</td>
<td>1000 mg</td>
<td></td>
</tr>
<tr>
<td>Vitamin D₃ 1000 IU</td>
<td></td>
<td></td>
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</tbody>
</table>

*p=0.711  *p=0.039  *p=0.040

*Fisher Exact Test
Comparison of Characteristics of Cohorts A, B and C

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Weight (kg) (mean ± SD)</th>
<th>Blood volume (mL) (mean ± SD)</th>
<th>Age (yr) (mean ± SD)</th>
<th>**p&lt;0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>85.6 ± 1834</td>
<td>5361 ± 870</td>
<td>53.9 ± 13.8</td>
<td>‡ ‡</td>
</tr>
<tr>
<td>B</td>
<td>86.8 ± 19.8</td>
<td>5386 ± 908</td>
<td>51.4 ± 10.4</td>
<td>‡ §</td>
</tr>
<tr>
<td>C</td>
<td>83.3 ± 16.1</td>
<td>5192 ± 765</td>
<td>62.7 ± 8.9</td>
<td>‡ §</td>
</tr>
<tr>
<td></td>
<td>*p=0.935</td>
<td>*p=0.819</td>
<td>*p=0.007</td>
<td></td>
</tr>
</tbody>
</table>

*Kruskal-Wallis One Way Analysis of Variance on Ranks

**Dunn’s Pairwise Multiple Comparison Procedure: ‡ = no; § = yes
Age Range Not a Factor in the Occurrence of Hypocalcemic Toxicity

| Study Subjects Reporting Symptoms of Hypocalcemic Toxicity: Sorted by Age Range |
|---------------------------------|-----------------|-----------------|-----------------|
| Age                             | Male            | Female          | Overall         |
| > 50 years                      | 12 of 7 (32.4%) | 6 of 12 (50%)  | 18 of 49 (36.7%)|
| ≤ 50 years                      | 3 of 7 (42.9%)  | 2 of 5 (40%)   | 5 of 12 (41.7%) |

Comparison of age ranges by Fisher Exact Test

\[ p = 0.675 \quad p = 1.000 \quad p = 0.751 \]
Why Would Calcium Citrate be More Effective Prophylaxis than Calcium Carbonate?

• Absorption: calcium citrate > calcium carbonate
• Liquid supplement versus solid wafers
• Vitamin D₃ to enhance GI absorption
• Dissociation of plasma [Ca²⁺] from symptoms.
  – Symptoms prevented or alleviated without rise in [Ca²⁺]
  – Placebo effect of supplemental calcium?
  –
[Ca^2+] vs Citrate Accumulation During Platelet Donation

Time (minutes)

25 Platelet Donors

Total Blood Volume (L)  ACD-A (mL/min)
- 4.0 ± 0.3  5.0 ± 0.4
- 4.5 ± 0.4  5.8 ± 0.05
- 5.0 ± 0.4  6.6 ± 0.5

10 mL of 10% CaGlu IV over 15 minutes

Summary & Conclusions

• Liquid CaCit/CaPhos + Vit D₃
  – Prevents symptoms of hypocalcemic toxicity
  – More effective than calcium carbonate

• Can the regimen be further improved?
  – Dose? Frequency of dosing?
  – Other oral calcium supplements (glutarate, gluconate)?

• Effect on bone metabolism?

• Point-of-Care test for [Ca²⁺]
  – Monitor donors
  – Evaluate Ca+D formulations
Division of Transfusion Medicine

Thank You!