Citrate, Calcium and Magnesium metabolism and related toxicities

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Disclosure of Relevant Financial Relationships

- Hans None
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Adverse reactions

(Related to donor and patient apheresis)
Long term effects of apheresis procedures

• Comparison bone density of 45 donors >100 PLT-apheresis with 40 donors <50 procedures.
• 35% of >100 procedures donors showed significant osteoporosis.

Dettke J. Clin Apheresis 2003
Long term effects in frequent plt donors?

![Graph showing bone mineral density (Z-Score) for lumbar spine, total hip, and femoral neck.](image)

- Lumbar spine: P = 0.038
- Total hip: P = 0.36
- Femoral neck: P = 0.72

Calcium in urine

Comparison of urinary calcium excretion. Excretion of urinary calcium increase after citrate intervention. *P = 0.034

Tri-sodiumcitrate and calcium

![Chemical Structure](http://4.bp.blogspot.com/-69-2fUgntos/T9UE0fnWxTI/AAAAAAAAMPG/XwbSSOWjNZs/s1600/Calcium.jpg)
Calcium

- 99% in the bones → calcium phosphate
  (± 24,500 mmol)

Extra cellular fluid: 22.5 mmol → 9 mmol in plasma (2.2 – 2.6 mmol/L)
Plasma calcium

Total calcium 2.2 – 2.6 mmol/L (9 - 10.5 mg/dL)

- Ionized (free) calcium 1.1 – 1.4 mmol/L (4.5 – 5.6 mg/dL)
- Remainder bound mainly to albumen (± 50%)
Function of Calcium

- Structural function → bones
- Signaling function → messenger for some hormones
- Enzymatic function → co-enzyme for clotting factors
- Function in transmission of nerve impulse
- Function in the contraction of muscles
- Stabilization of cellular membranes
Prevention of blood clotting by citrate

1914

Luis Agote

Albert Hustin
Citrate

- Trisodiumcitrate
  - Prevention of blood clotting in disposable / machine
  - Flavoring and buffering agent in drinks / food (E330)
  - Laxative
  - WHO “oral rehydration solution”
Citrate handling during apheresis procedures

- Tri-sodiumcitrate is added to whole blood in procedure specific ratio
- Citrate resolves completely in plasma
- Citrate chelates free Calcium and Magnesium
- Citrate returns to donor with plasma containing components
Serum calcium & citrate infusion

Bolan, Transfusion 2002
Calcium regulation

http://www.en.wikipedia.org
Low concentration of calcium in blood

Release of parathyroid hormone

- Efflux of calcium from bone
- Decreased loss of calcium in urine
- Enhanced absorption of calcium from intestine

Increased concentration of calcium in blood
Serum PTH, iCa and Citrate during plt apheresis

Serum PTH and Calcium

(a) Serum Ca level (mmol/l)
(b) Serum iPTH level (pg/ml)

Observation time points (minutes)

- Placebo
- Citrate

$t = -22.46, P < 0.0001$, as measured by AUC

Observation time points (minutes)

- Placebo
- Citrate

$t = 12.13, P < 0.0001$, as measured by AUC

Function of Calcium

- Structural function → bones
- Signaling function → messenger for some hormones
- Enzymatic function → co-enzyme for clotting factors
- Function in transmission of nerve impulse
- Function in the contraction of muscles
Hypocalcemia

• Decrease in ionized calcium results in increased excitability of neurons to the point of spontaneous depolarization.
Function of Calcium

- Structural function → bones
- Signaling function → messenger for some hormones
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- Function in transmission of nerve impulse
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Symptoms of citrate reactions

**Mild**
- Perioral or acral paresthesias
- Sneezing
- Lightheadedness
- Flushing
- Shivering
- Headaches

**Moderate**
- Nausea and vomiting
- Nervousness and irritability
- Abdominal cramping
- Involuntary muscle contraction: carpopedal spasm, tetany
- Tremors
- Hypotension

**Severe**
- Cardiac arrhythmias
- Seizures
Citrate

- Completely dissolved in plasma
- No binding to cells
- Chelates calcium and Magnesium
- Prevents coagulation

Neutralized by:
- Distribution throughout extra cellular fluid
- Excretion by the kidneys
- Rapid metabolism by the kidneys, liver and skeletal muscle

Jeff Winters, AABB Oct. 2007
Citrate → Metabolic Alkalosis

Additional factors to consider

- Presence of citrate in replacement fluids (e.g. FFP for TTP)
- Large volume PBSC collections (average drop Ca$^{2+}$ of 11.3±7%)
- Citrate → Bi-carbonate → Alkalosis

\[
\text{Citrate: } 3 \text{Na}^+ + \text{O}_3\text{C} \text{H}_2 \text{O}_3\text{C} + \text{H}^+ \rightarrow \text{Ca}^{2+} + 2 \text{Mg}^{2+} + \text{CO}_2 + \text{H}_2\text{O}
\]
Citrate → Metabolic Alkalosis & Hypokalemia

Additional factors to consider
- Presence of citrate in replacement fluids (e.g. FFP for TTP)
- Large volume PBSC collections (average drop Ca^{2+} of 11.3±7%)
- Citrate → Bi-carbonate → Alkalosis → excretion citrate ↑
- Renal disease preventing the excretion of bicarbonate and citrate
  → symptoms of hypocalcemia ↑, suppression of respiratory rate
  → Metabolic alkalosis

- Metabolic alkalosis results in potassium uptake in cells → hypokalemia
  Decrease in potassium and cardiac arrhythmia
Citrate

- Chelates calcium and Magnesium
Citrate → Hypomagnesemia

- Mg$^{2+}$ also bound by citrate
- During plateletapheresis: 30% drop in magnesium levels
Serum magnesium during plateletapheresis

Bolan, et al. Transfusion 2001;41:1165-1171
Plasma magnesium

Total magnesium 0.7 – 1.1 mmol/L (1.5 – 2.5 mg/dL)

• Ionized (free) magnesium 0.5 – 0.7 mmol/L (1.1 – 1.5 mg/dL)
• Remainder bound mainly to Albumen and globulins
Magnesium

Involved in:
• Synthesis of nucleic acids
• Synthesis of proteins
• Intermediary metabolism
• Specific actions in
  • Neuromuscular systems
  • Cardiovascular systems

$\text{Mg}^{2+}$ competes with $\text{Ca}^{2+}$ for binding sites on proteins and membranes

Competitively inhibition of calcium
Magnesium

Affects:
- Muscular contraction and relaxation including the heart and vascular muscles.
- Electrical activity of myocardial cells
- Stabilization of the axon
- The release of neurotransmitters
Hypomagnesaemia

Caused by
• Redistribution of Mg
• Gastrointestinal
• Renal loss
• Renal disease
• Endocrinal
• Diabetes mellitus
• Alcoholism
• Miscellaneous

• Drugs
  • Diuretics
  • Cytotoxic drugs
  • Antibiotics
  • B adrenergic agents
  • Others
**Hypomagnesaemia**

- Citrate and hypocalcaemia

### Electrolyte disturbance
- Hypokalaemia
- Hypocalcaemia

### Neuromuscular and central nervous system
- Carpopedal spasm
- Convulsions
- Muscle cramps
- Muscle weakness, fasciculations, tremors
- Vertigo
- Nystagmus
- Depression, psychosis
- Athetoid movements & choreiform movements

### Cardiovascular
- Atrial tachycardias, fibrillation
- Supraventricular arrhythmias
- Ventricular arrhythmias
- Torsade de pointes
- Digoxin sensitivity

### Complications of magnesium deficiency
- Altered glucose homeostasis
- Atherosclerotic vascular disease
- Hypertension
- Myocardial infarction
- Osteoporosis

### Miscellaneous
- Migraine
- Asthma
- Chronic fatigue syndrome
- Impaired athletic performance
Citrate → Hypomagnesemia

- Mg\(^{2+}\) also bound by citrate
- During plateletapheresis: 30% drop in magnesium levels
- Steeper decrease and recovers more slowly than calcium
- Muscle spasms & weakness
- Decreased vascular tonus (blood pressure) + abnormal cardiac contractility
- Interference with potassium and calcium homeostasis
- If suspected 8 mmol Mg\(^{2+}\) i.v. in 1 minute
In Summary

- For apheresis procedures we use citrate solutions
- Citrate is binding calcium and magnesium
- Citrate is returned to the donor
- Hypocalcemia and hypomagnesemia \(\rightarrow\) effects
- Direct (side) effects of citrate
Adverse reactions

(Related to donor and patient apheresis)
For information


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