Hypocalcemia or Not?

Lies A.L. Fliervoet [a,*] Hans Kemperman [a] Stephanie M. van der Leij,[b] and Wouter M. Tiel Groenestege[a]

Case Description

A 69-year-old woman receiving treatment with leflunomide for rheumatoid arthritis was admitted for a pacemaker upgrade, which was complicated by *Staphylococcus aureus* bacteremia. Laboratory results showed severe hypocalcemia—ionized calcium (iCa) of 0.66 mmol/L (2.6 mg/dL) (reference interval 1.15–1.32 mmol/L; 4.6–5.3 mg/dL), which prompted treatment with intravenous calcium. The physician was confused, however, by the very low iCa without clinical manifestations of hypocalcemia and contacted the laboratory. Results of subsequent iCa analyses on 4 different analyzers are shown in Fig. 1.

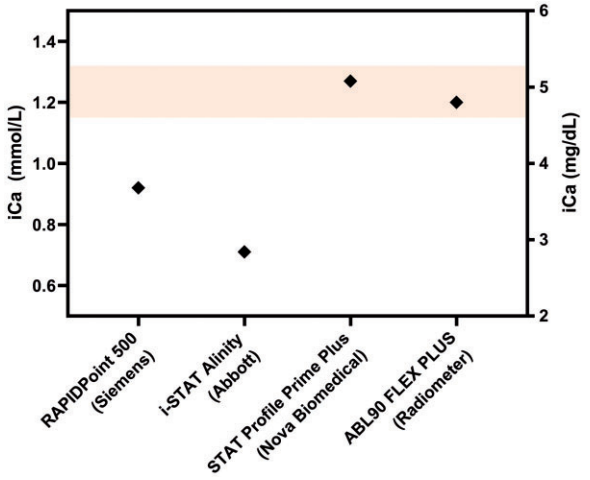

Fig. 1. Results of ionized calcium (iCa) from subsequent sample obtained with 4 different types of analyzer. Shaded area indicates reference interval (1.15–1.32 mmol/L; 4.6–5.3 mg/dL). Total calcium was 2.29 mmol/L (9.2 mg/dL) with a reference interval of 2.20–2.60 mmol/L (8.8–10.4 mg/dL).

Questions

- What is the most likely cause of hypocalcemia observed with RAPIDPoint and i-STAT Alinity?
- How could you confirm your suspicion?
- Which substances can cause clinically relevant analytical interference of iCa?

[a]Central Diagnostic Laboratory, University Medical Center Utrecht, Utrecht, the Netherlands
[b]Internal Medicine, University Medical Center Utrecht, Utrecht, the Netherlands
*Address correspondence to this author at: Central Diagnostic Laboratory, University Medical Center Utrecht, Heidelberglaan 100, 3584 CX Utrecht, the Netherlands. Internal mail no. G03.550, Rm. G03.422, P.O. Box 85500, 3508 GA Utrecht, the Netherlands. E-mail l.a.l.fliervoet-2@umcutrecht.nl.
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The answers are below.

Leflunomide can interfere with iCa measurement resulting in falsely decreased values (1), most likely related to the specific structure of the iCa-selective electrode used. A similar effect is seen with perchlorate, a thyroid blocking agent (2). To confirm analytical interference by leflunomide, iCa could be measured on an analyzer not affected by this interferent. Additionally, evaluation of total calcium in these patients can be helpful. Awareness of this interference can prevent inappropriate and potentially harmful calcium treatment.

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References

1. Verhoeven Y, Kemperman H, Abrahams AC. Falsely decreased ionized calcium levels in kidney transplant recipients with polyomavirus-associated nephropathy treated with leflunomide. Transpl Int 2015;28:874–5.
2. Gruber M, Nehring C, Creutzenberg M, Graf B, Hopf S. Perchlorate (Irenat®) may falsely lower measured ionised calcium. Clin Chem Lab Med 2011;49:1019–24.