

Letter to the Editor

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Perchlorate interference with electrolyte analysis

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To the Editor,

The clinical chemist has a pivotal role in recognizing analytical interference of medication in diagnostic laboratory assays [1, 2]. Timely signaling of interference can lead to a reduction in diagnostic errors and therefore to increased patient safety and quality of care. In our hospital, a 26-year-old man presented with amiodarone-induced thyrotoxicosis (TSH < 0.015 mIU/L, FT4 > 77 pmol/L), for which a combined therapy of thiamazole (Strumazol 30 mg, one time each day) and sodium perchlorate (500 mg, two times each day) was started (written consent was obtained from the patient). Soon afterward unexplainably low sodium (Na⁺) and ionized calcium (Ca²⁺) concentrations were obtained, which prompted the endocrinologist to contact the laboratory, not sure whether electrolyte treatment should be started. The concentrations, measured on the RAPIDPoint 500 blood gas analyzer (Siemens Healthineers, Erlangen, Germany), were highly discrepant with the results of the AU5811 chemistry analyzer (Beckman–Coulter, Brea, CA, USA). Na⁺ levels were about 10 mmol/L lower at RAPIDPoint 500 (Figure 1). In addition, ionized Ca²⁺ levels as low as 0.5 mmol/L (reference interval: 1.15–1.32 mmol/L) were reported, while total calcium levels were normal.

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Perchlorate is a potent competitive inhibitor of the sodium/iodide symporter, which is used in the perchlorate discharge test to identify organification defects and for treating amiodarone-induced thyrotoxicosis type I [3]. Interference of perchlorate with ionized Ca²⁺ measurements has been described before for several blood gas analyzers, but no effects on Na⁺ levels were mentioned [4, 5]. Therefore, we compared electrolyte measurements at RAPIDPoint 500 and AU5811 in the presence of a range of perchlorate concentrations. As many wards in our hospital rely on i-STAT point-of-care analyzers (Abbott Laboratories, Chicago, IL, USA) for electrolyte measurements, we also included this analyzer in our comparison.

Sodium perchlorate concentrations *in vivo* depend on dose, intake frequency, distribution volume and kidney function. In 11 patients receiving perchlorate, plasma concentrations ranging from 0.031 to 2.75 mmol/L were obtained by Gruber et al. using a perchlorate-selective electrode [5]. Therefore, we decided to analyze sodium, potassium (K⁺), chloride (Cl⁻) and calcium (RAPIDPoint/i-STAT: ionized Ca²⁺; AU5811: total calcium) levels in the presence of perchlorate with plasma concentrations ranging from 0.05 to 4 mmol/L (sodium perchlorate was dissolved and diluted). We used pooled anonymous left-over blood samples (BD Vacutainer lithium heparin 4.0 mL) for which a maximal pH difference of 0.05 within 1 dilution series (max. 0.03 mmol/L ionized Ca²⁺) was allowed. RAPIDPoint 500 and i-STAT analyses were performed in whole blood, while AU5811 analyses were carried out in derived plasma. The measured Na⁺ levels were corrected for the added amount as part of sodium perchlorate.

Perchlorate levels of 1 mmol/L and higher induced clinically significant decreases of the Na⁺ concentration when measured on RAPIDPoint 500 (Figure 2A). At 4 mmol/L, perchlorate caused 11.5 mmol/L (8.2%) reduction of the Na⁺ concentration (Supplementary Figure 1A). Na⁺ measurements at i-STAT and AU5811, however, were hardly influenced by perchlorate. Cl⁻ levels at RAPIDPoint 500 significantly increased in response to perchlorate, with a maximal increase of 21.3 mmol/L, while AU5811 Cl⁻ levels only showed a minor rise (Figure 2B, Supplementary Figure 1B). Perchlorate interference with i-STAT Cl⁻ analysis was not investigated, because the CG8+ cartridge used in

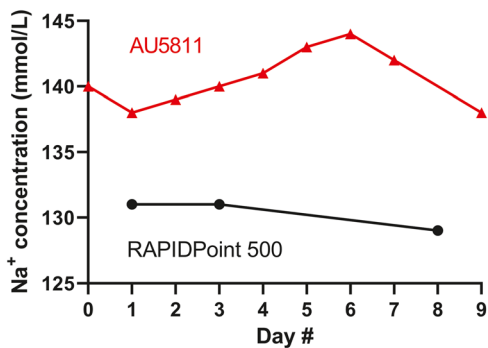


Figure 1: Na⁺ levels measured for the patient described in the introductory paragraph receiving sodium perchlorate. Sodium perchlorate therapy was started 5 days before the first Na⁺ measurement was performed (on day 0), and was continued till day 6.

our hospital for electrolyte and blood gas analyses does not support Cl⁻ measurement. The cartridge that includes the Cl⁻ electrode (EC8+) is not in use in our country. The large effect of perchlorate on ionized Ca²⁺ measurements using RAPIDPoint 500 was similar to that reported before for related Siemens blood gas analyzers (Figure 2C,

Supplementary Figure 1C) [4, 5]. The i-STAT ionized Ca²⁺ measurements were only slightly less affected by perchlorate. AU5811 total calcium levels were stable over all perchlorate levels (Supplementary Figure 2). K⁺ was found to be the least perchlorate-sensitive parameter of RAPIDPoint 500, although 4 mmol/L perchlorate induced a 5.4% decrease (Figure 2D, Supplementary Figure 1D). i-STAT K⁺ levels showed a larger reduction (6.9%), while AU5811 measurements remained fully stable. The interference of perchlorate with electrolyte analysis at RAPIDPoint 500 was observed despite the so-called “retrocal” mode (internal compensation mechanism of the blood gas analyzer when possible interference is detected) being active.

If a patient receives perchlorate therapy, the i-STAT is a good alternative for RAPIDPoint 500 to measure Na⁺ levels using the commonly applied CG8+ cartridge. In addition, all studied electrolytes can be reliably measured on AU5811, with the exception of Cl⁻ in the presence of 4 mmol/L perchlorate. For calcium, measurement of the total level on AU5811 is the most reliable option. Alternatively, a perchlorate-insensitive direct ISE (ion-selective

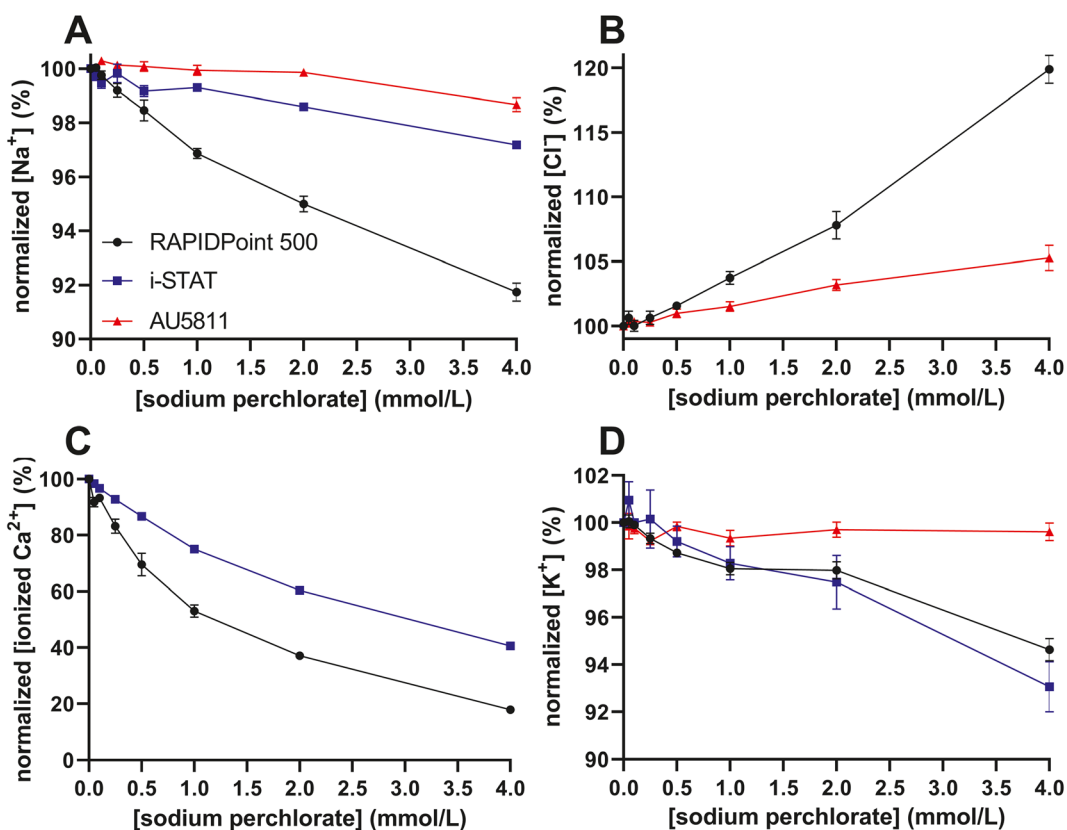


Figure 2: Normalized Na⁺ (A), Cl⁻ (B), ionized Ca²⁺ (C), and K⁺ (D) levels measured in sodium perchlorate-spiked whole blood or derived plasma (electrolyte level in absence of perchlorate=100%). Measurements were performed at RAPIDPoint 500, i-STAT and AU5811. Sodium perchlorate concentrations are reported as plasma levels (corrected for hematocrit as spiking was performed in whole blood). All values are presented as means of measured concentrations ± SEM (standard error of mean) from n=3 independent experiments.

electrode) method may be used [5]. In contrast to many other situations (e. g., pseudohyponatremia), analysis using indirect ISE is less sensitive to perchlorate than some direct ISE methods, probably because its 10× dilution step decreases the amount of perchlorate in the measuring cell. Up to now, however, there is no evidence that Na⁺ and Cl⁻ analyses of other direct ISE methods are susceptible to perchlorate interference.

The RAPIDPoint 500 Na⁺ and Cl⁻ electrodes were found to be fairly sensitive to perchlorate. Interestingly, in previous reports no effect of perchlorate on Na⁺ or Cl⁻ measurements of Siemens RAPIDPoint 405, RAPIDLab 405 and RAPIDLab 865 blood gas analyzers was mentioned [4, 5]. Only a few substances were reported to interfere with Na⁺ measurements on blood gas analyzers, such as benzalkonium heparin and nortriptyline [6, 7]. The interference of nortriptyline was only observed for RAPIDPoint 500 and was specific for Na⁺ [7]. The authors suggested that the Na⁺-selective ionophore in the membrane of the electrode was also susceptible to nortriptyline. Selectivity issues of Cl⁻ electrodes containing quaternary ammonium or phosphonium salts as anion exchangers are a known phenomenon. The selectivity of the Cl⁻ electrode is determined by the relative free solvation energy, which is more favorable for anions with a higher polarizability or lipophilicity such as bromide, iodide, nitrate, thiocyanate, salicylate and bicarbonate [8]. As part of medication these components can lead to falsely increased Cl⁻ levels. Perchlorate, being much more lipophilic than chloride, can also interfere with potentiometric Cl⁻ analysis [9]. These selectivity issues may have caused the observed perchlorate interference on Na⁺ and Cl⁻ analyses, although the exact composition of RAPIDPoint 500 electrodes is unknown.

Perchlorate interference leads to a combined decrease of Na⁺ and increase of Cl⁻ levels when measured at RAPIDPoint 500, which makes a calculated anion gap highly unreliable. Even a negative anion gap may be obtained, but more subtle, a falsely declined anion gap may hide the presence of a clinically relevant anion fraction. Only sequential analysis of the electrolyte concentrations using different analyzers or measurement of the osmolality will reveal the erroneous result. Moreover, inappropriate correction of electrolyte levels can negatively impact patients' health. Therefore, knowing the sensitivity of each of the electrolyte analyzers on one's laboratory to perchlorate is highly relevant.

Based on our perchlorate titration data, the patient's *in vivo* sodium perchlorate plasma concentration probably was ~4 mmol/L. This level is higher than found

before, and much higher than ~0.3 mmol/L which can be calculated from a 1,000 mg dose each day and distribution volume of 0.34 L/kg [5, 10]. As perchlorate is excreted by the kidneys (half-life~7.5 h), the high *in vivo* concentration may be related to the decreased kidney function of the patient – known with Becker muscular dystrophy – who was suffering from myositis during the thyrotoxic phase [10].

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References

1. Plebani M. Diagnostic errors and laboratory medicine – causes and strategies. *eJIFCC* 2015;26:7–14.
2. Van Balveren JA, Verboeket-Van de Venne WP, Erdem-Eraslan L, De Graaf AJ, Loot AE, Musson RE, et al. Impact of interactions between drugs and laboratory test results on diagnostic interpretation – a systematic review. *Clin Chem Lab Med* 2018;56:2004–9.
3. Martino E, Aghini-Lombardi F, Mariotti S, Lenziardi M, Baschieri L, Braverman LE, et al. Treatment of amiodarone associated thyrotoxicosis by simultaneous administration of potassium perchlorate and methimazole. *J Endocrinol Invest* 1986;9:201–7.
4. Durner J, Winkler-Budenhofer U, Gahr S, Samtleben W, Schönermark U. Pseudohypocalcemia caused by perchlorate (Irenat). *Clin Chem Lab Med* 2011;49:665–7.
5. Gruber M, Nehring C, Creutzenberg M, Graf B, Hopf S. Perchlorate (Irenat) may falsely lower measured ionized calcium. *Clin Chem Lab Med* 2011;49:1019–24.
6. Koch TR, Cook JD. Benzalkonium interference with test methods for potassium and sodium. *Clin Chem* 1990;36:807–8.
7. Van der Hagen EA, Smeekens KC, Van 't Veer NE, Boonen KJ, Ermens AA. Interference in Na⁺ measurements on the Siemens RAPIDPoint 500 after nortriptyline intoxication: a case report. *Clin Chem Lab Med* 2017;55:e199–201.
8. Dimeski G, Badrick T, St John A. Ion selective electrodes (ISEs) and interferences – a review. *Clin Chim Acta* 2010;411:309–17.
9. Gemene KL, Shvarev A, Bakker E. Selectivity enhancement of anion-responsive electrodes by pulsed chronopotentiometry. *Anal Chim Acta* 2007;583:190–6.
10. Crump KS, Gibbs JP. Benchmark calculations for perchlorate from three human cohorts. *Environ Health Perspect* 2005;113:1001–8.

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