

Pseudohypocalcemia caused by perchlorate (Irenat[®])

Jürgen Durner¹, Ursula Winkler-Budenhofer²,
Simon Gahr², Walter Samtleben² and
Ulf Schönermarck^{2,*}

¹ Institute of Clinical Chemistry, University Hospital
Munich-Grosshadern, Ludwig-Maximilians-University,
Munich, Germany

² Nephrology Division, Department I of Internal Medicine,
University Hospital Munich-Grosshadern, Ludwig-
Maximilians-University, Munich, Germany

Abstract

Background: Blood gas analysis (BGA), including measurement of ionized calcium, is performed routinely in patients with end stage renal disease on renal replacement therapy, especially when using citrate for regional anticoagulation. After installation of a new blood gas analyzer (RAPIDpoint[®] 405; BGA), we observed lower ionized calcium concentrations in a few patients without signs of hypocalcemia, whereas calcium concentrations were normal using a standard laboratory method. Pseudohypocalcemia was of limited duration and correlated with the short-term intake of sodium perchlorate monohydrate (Irenat[®]).

Methods: We prepared dilution series from whole blood samples and stock solutions of calcium and perchlorate with different concentrations of ionized calcium and perchlorate. Measurement of ionized calcium concentrations was performed using two different blood gas analyzers (RAPIDpoint[®] 405; BGA and Roche AVL 9180; standard laboratory method).

Results: After addition of different amounts of perchlorate, significant lower ionized calcium concentrations were measured with BGA compared to the standard laboratory method using either preparations from whole blood samples or stock solutions. The addition of potassium or methylene blue known to complex perchlorate had no effect on the concentrations of ionized calcium measured with BGA. Using different mathematical methods, a calculation of the “real” ionized calcium concentration from the value measured with BGA was not possible.

Conclusions: Based on our experiments, we confirm the hypothesis that perchlorate can influence the measurement of ionized calcium by BGA. As the effect depends on the ion selective electrode that is used, it is advisable to test the blood gas analyzer with calcium and perchlorate solutions.

*Corresponding author: Ulf Schönermarck, MD, Department I of Internal Medicine, Nephrology Division, University Hospital Munich, Campus Grosshadern, Ludwig-Maximilians-University Munich, Marchioninstr. 15, 81377 Munich, Germany
Phone: +49-89-7095-2212, Fax: +49-89-7095-5317,
E-mail: ulf.schoenermarck@med.uni-muenchen.de
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Introduction

Blood gas analysis (BGA), including measurement of acid-base status, electrolytes and ionized calcium is regularly performed in patients with end stage renal disease (ESRD) undergoing regular intermittent hemodialysis treatment or patients with acute renal failure on continuous renal replacement therapy. The frequent measurement of ionized calcium is even more essential when using citrate for regional anticoagulation in patients with high-risk of bleeding.

During the past few years, ionized calcium concentrations were measured in our hospital bedside with a point-of-care BGA system using ion selective electrodes (ISEs). After changing to another BGA device, we observed in a few patients with ESRD on regular hemodialysis treatment, a sudden and unexpected development of very low concentrations of ionized calcium, although these patients showed no clinical signs of hypocalcemia (Table 1). When checking the calcium concentrations by our hospital laboratory that used standard laboratory methods, normal concentrations of ionized and total calcium were found, suggesting that the pseudohypocalcemia measured with the BGA was probably due to an interfering substance. Furthermore, we observed an increase in ionized calcium concentrations during each hemodialysis session in these patients. Viewing the medication list, we noticed a temporal relationship with the development of hypocalcemia and the intake of sodium perchlorate monohydrate (Irenat[®]). Therefore, we tested the hypothesis that perchlorate might influence the measurement of ionized calcium in our new BGA system.

Materials and methods

A stock solution of calcium gluconate (B. Braun, Melsungen, Germany) was prepared with 0.9% NaCl (B. Braun) at a concentration of 2.5 mmol/L ionized calcium. A stock solution of sodium perchlorate monohydrate (Irenat[®]; Bayer, Leverkusen, Germany) was prepared with 0.9% NaCl at a concentration of 2.45 mmol/L perchlorate (ClO₄⁻). Under the assumption that a patient with a weight of 75 kg and a blood volume of 6 L received 45 drops Irenat[®] orally, which were completely absorbed, and that perchlorate has a volume of distribution of 0.34 L/kg (1), a serum perchlorate concentration of 0.3 mmol/L can be estimated. Higher serum concentrations would be expected with higher doses, a lower volume of distribution, repeated drug dosing and accumulation due to renal insufficiency.

Measurement of ionized calcium was performed with a RAPIDpoint[®] 405 Blood Gas Analyzer (Siemens Healthcare Diagnostics, Munich, Germany; referred to as BGA) and with a Roche AVL 9180

Table 1 Blood samples from three patients with end-stage renal disease on regular hemodialysis treatment receiving perchlorate for a short period of time because of a radiologic examination with iodine-containing contrast medium. The ionized and total calcium concentrations were measured before, during and after perchlorate intake with the routine laboratory method (Lab) compared to the blood gas analyzer RAPIDpoint® 405 (BGA).

Patient	Before		During			After	
	Ionized Ca ²⁺ (BGA), mmol/L		Ionized Ca ²⁺ (BGA), mmol/L		Perchlorate intake Ionized Ca ²⁺ (Lab), mmol/L	Total Ca ²⁺ (Lab), mmol/L	
1	1.05		0.33		0.91	1.70	
2	1.09		0.49		1.17	2.01	
3	1.15		0.42		1.20	2.43	

Electrolyte Analyzer from the routine laboratory in our hospital (Roche Diagnostics, Basel, Switzerland; laboratory method). Both systems measure ionized calcium with an ISE.

In the first set of experiments, different concentrations of ionized calcium and perchlorate were prepared by mixing the stock solutions. The obtained concentrations are given in Table 2. In a second set of experiments, native whole blood samples from two healthy volunteers, taking no pharmaceuticals, were mixed with the perchlorate stock solution to obtain the concentrations given in Table 2. In a third set of experiments, KCl (concentration of stock solutions: 4.0 mmol/L, 1.0 mol/L or 4.4 mol/L) or methylene blue (saturated solution) (Merck, Darmstadt, Germany) were added to samples with ionized calcium and perchlorate. From both substances it is known that they can complex perchlorate (2, 3). In a fourth set of experiments, dilution series from stock solutions of ionized calcium and perchlorate were prepared.

The measured ionized calcium values from BGA and laboratory method were analyzed with different mathematical models (formation of quotients, exponential regression, polynomial regression) to determine a correction algorithm.

Statistical analysis of significance was performed using the paired sample t-test, corrected according to Bonferroni-Holm. $p < 0.05$ was

considered to be significant. All values are presented as means of the measured ionized calcium \pm SD (standard deviation) from $n = 4$ independent experiments.

Results

After preparation of samples with different concentrations of ionized calcium and perchlorate, significant lower concentrations of ionized calcium were measured with BGA compared to the laboratory method (Table 2A). At ionized calcium concentrations of 0.8 and 1.0 mmol/L and at the lowest tested perchlorate concentration (0.075 mmol/L), significant lower ionized calcium concentrations were measured with BGA compared to the laboratory results (Table 2A). Multiple measurements lead to the same results within the limits of ionized calcium measurements of 7.5%, with respect to the guidelines of the German Medical Association Panel for Quality Control in Medical Laboratory Investigations (4).

Table 2 Measured ionized calcium concentrations with the laboratory method (Lab) compared to the blood gas analyzer RAPIDpoint® 405 (BGA). Samples contain different concentrations of ionized calcium and perchlorate. Data are shown as the mean. The CV was $< 7.5\%$ and is not included in order to simplify the Table. ^aSignificant differences between measured and expected ionized calcium concentrations.

(A) The concentration of ionized calcium in the sample from stock solution is listed in column one (expected Ca²⁺). The concentration of perchlorate in the sample is listed in row two.

Expected Ca ²⁺ , mmol/L	Perchlorate, mmol/L											
	1.2		0.9		0.6		0.3		0.15		0.075	
	Lab	BGA	Lab	BGA	Lab	BGA	Lab	BGA	Lab	BGA	Lab	BGA
0.8	0.84	0.28 ^a	0.85	0.34 ^a	0.84	0.44 ^a	0.84	0.56 ^a	0.88	0.66 ^a	0.85	0.64 ^a
1.0	1.02	0.44 ^a	1.02	0.21 ^a	1.04	0.25 ^a	1.02	0.67 ^a	1.02	0.79 ^a	1.01	0.87
1.2	1.20	0.29 ^a	1.22	0.51 ^a	1.20	0.68 ^a	1.14	0.92 ^a	1.20	1.11	1.2	1.25
1.4	1.38	0.45 ^a	1.37	0.56 ^a	1.37	0.44 ^a	1.38	1.00 ^a	1.37	1.22	1.37	1.38

(B) The concentration of ionized calcium in whole blood samples from two healthy donors is listed in column one (expected Ca²⁺). The same amounts of perchlorate were added as in (A). Because perchlorate likely will not reach equilibrium across the red blood cell membrane very quickly, the plasma concentration of perchlorate in the sample is higher. The effective plasma concentration of perchlorate after volume correction of whole blood samples according to the hematocrit is listed in row two.

Expected Ca ²⁺ , mmol/L	Perchlorate, mmol/L											
	2.3		1.7		1.1		0.6		0.29		0.143	
	Lab	BGA	Lab	BGA	Lab	BGA	Lab	BGA	Lab	BGA	Lab	BGA
1.26 (Donor 1)	1.27	0.34 ^a	1.29	0.50 ^a	1.30	0.64 ^a	1.31	0.63 ^a	1.31	0.75 ^a	1.33	1.06 ^a
1.20 (Donor 2)	1.27	0.26 ^a	1.29	0.37 ^a	1.29	0.53 ^a	1.32	0.76 ^a	1.31	0.96 ^a	1.33	1.06 ^a

A similar result was obtained using whole blood samples from two healthy volunteers. Donor 1 had an ionized calcium of 1.26 mmol/L and donor 2 of 1.20 mmol/L measured with the BGA. The hematocrit was 48% in donor 1 and 47% in donor 2. After addition of different amounts of a concentrated perchlorate stock solution to whole blood samples, significant lower ionized calcium concentrations were measured with BGA compared to the laboratory result (Table 2B). The measurement of sodium and potassium with both BGA and the laboratory method was not influenced by addition of perchlorate.

The addition of various concentrations of potassium as well as the addition of a saturated solution of methylene blue had no effect on the concentrations of ionized calcium measured with the BGA and were therefore not able to normalize the measured calcium concentrations (data not shown).

Analyzing the measured values from BGA and the routine laboratory method with different mathematical models, it was not possible to find a correction factor or an algorithm to calculate the “real” ionized calcium value from the measured one with the BGA.

Discussion

After implementation of a new BGA device using a different ISE (RAPIDpoint® 405), we noticed a temporal profound reduction in ionized calcium concentrations in a few patients with ESRD on regular hemodialysis treatment. These patients showed no clinical signs of hypocalcemia and had previously normal ionized calcium concentrations. Measurement of ionized and total calcium concentrations with the routine laboratory method revealed normal results, although both analyzing systems used ISEs. Therefore, pseudohypocalcemia was diagnosed which was of limited duration and correlated well with the prescription of sodium perchlorate monohydrate.

Perchlorate (Irenat®) is widely used to prevent thyroid dysfunction after administration of iodine-containing contrast medium (5). Studies in humans and animals revealed that perchlorate is excreted unchanged via the kidney, with a half-life of approximately 6 h (6, 7). Therefore, in renal insufficiency, perchlorate can accumulate, although usually without side effects during short-term application.

The results of our experiments verified the hypothesis that sodium perchlorate influences the measurement of ionized calcium in the BGA (RAPIDpoint® 405) that we used. We could show that this effect was measurable even at very low perchlorate concentrations, which are easily achieved in patients with accumulation of perchlorate due to renal insufficiency. Meanwhile, a similar, but less pronounced disturbance of ionized calcium measurements has also been noted with certain blood gas analyzing systems from a different manufacturer. Without knowledge of the specific structure of the membrane used in different ISE, the mechanisms of interference with perchlorate remain unclear.

In the dilution series with different concentrations of ionized calcium and perchlorate, we could show that it is not

possible to find a simple correction factor or an algorithm to calculate the “real” ionized calcium concentration from the measured value with our BGA system. The observed increase in ionized calcium concentrations during each hemodialysis session can be explained by the fact that perchlorate was removed during hemodialysis (8). Furthermore, we were not able to antagonize the perchlorate effect in the blood samples with the addition of potassium or methylene blue, which have been used to measure perchlorate by forming sparingly soluble complexes (2, 3).

In summary, unexplained hypocalcemia in BGA should prompt the clinician to search for possible interacting substances. Our study supports the hypothesis that sodium perchlorate (Irenat®) can interfere with the measurement of ionized calcium. The effect depends on the ISE used in the analyzing system. A calculation of the “real” ionized calcium concentration from the value measured with BGA is not possible. Thus, it is advisable to test the analyzing system on the clinical ward with stock solutions of ionized calcium (in the range of 1.0–1.4 mmol/L) and perchlorate (0.6–1.2 mmol/L) to see if the measurement of ionized calcium is affected.

Conflict of interest statement

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