

EXCEPTIONAL CASE

Pseudohypobicarbonatemia in a patient with amyloidosis

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ABSTRACT

We report a case of a patient who had critically low serum bicarbonate (HCO_3^-) levels ranging from 8 to 11 mmol/L on repeated venous measurements using an enzymatic/photometric assay. This prompted hospitalization and treatment with intravenous sodium bicarbonate (NaHCO_3) followed by oral NaHCO_3 . He was evaluated for potential causes of high anion gap metabolic acidosis without any etiology found. He continued to have low serum HCO_3^- levels despite maintenance oral NaHCO_3 therapy and was referred for a second opinion where further laboratory work was pursued. An arterial blood gas was obtained, which revealed normal whole blood pH and HCO_3^- levels. A different enzymatic/photometric assay revealed a normal serum HCO_3^- level at 21 mmol/L. Additional workup revealed paraproteinemia, which was thought to interfere with the enzymatic process by which his serum HCO_3^- was measured, resulting in erroneous values.

Keywords: paraproteinemia, pseudohypobicarbonatemia

INTRODUCTION

The first step in the diagnosis of an acid–base disorder is obtaining accurate measurement of blood bicarbonate (HCO_3^-), pH and partial pressure of carbon dioxide (pCO_2) levels. Blood HCO_3^- levels are commonly estimated via two methods: direct measurement of serum total carbon dioxide (TCO_2) or calculation of the Henderson–Hasselbalch equation using arterial whole blood and directly measuring pH and pCO_2 levels using a blood gas analyzer [1–3]. For the first method, TCO_2 is used as an estimate of the serum HCO_3^- level, as 95% of the TCO_2 in the blood is in the form of HCO_3^- [1, 2]. The serum TCO_2 is measured on automated chemistry analyzers using blood samples by either of two methods: enzymatic/photometric assay or an electrode-based method [1, 2].

When using the enzymatic method to measure serum HCO_3^- levels, photometric analysis is used. This can be affected by any substance that would potentially interfere with the steps

of the enzymatic reaction or the light absorbance measured by photometry [4, 5]. There have been instances reported of falsely low serum HCO_3^- levels due to interference by elevated triglyceride levels [6–8], but only two cases to our knowledge have been reported of spuriously low serum HCO_3^- levels secondary to interference by paraproteins [6, 9].

CASE REPORT

A 74-year-old male with past medical history of bladder carcinoma *in situ* on Bacillus Calmette–Guérin treatment, hypertension and hyperlipidemia presented with complaints of malaise and flu-like symptoms after a recent bladder irrigation. He was found to have unremarkable labs except for a serum HCO_3^- level of 8 mmol/L measured using a Siemens Vista (SV) 500 enzymatic automated chemistry analyzer with an anion gap of 22. Repeat levels were drawn on the same day with resultant

Received: 21.2.2022; Editorial decision: 1.4.2022

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serum HCO_3^- levels of 8 and 9 mmol/L. A venous blood gas was also obtained on the same day with normal pH 7.41 and venous pCO_2 of 39; however, the HCO_3^- level was not reported. The patient was hospitalized for acute high anion gap metabolic acidosis (HAGMA). Nephrology was consulted and he was started on intravenous sodium bicarbonate (NaHCO_3 ; dextrose 5% with water and 150 mEq/L of NaHCO_3). A repeat serum HCO_3^- level was 11 mmol/L the following day with subsequent transition to oral NaHCO_3 650 mg thrice daily and discharge to home on the patient's insistence. Admission lab work had been notable for serum creatinine 1.17 mg/dL, potassium 4.0 mmol/L, osmolar gap 3, lactate 0.8 mmol/L, negative blood/urine cultures and negative aspirin and acetaminophen levels. Notably, his serum triglycerides were also checked on two separate occasions during this time and they were within normal limits. The etiology of HAGMA was unclear and presumed secondary to his recent bladder irrigation.

On outpatient follow-up, the patient continued to have low serum HCO_3^- levels ranging from 8 to 11 mmol/L (results from the same facility using an SV analyzer) despite his reported compliance with NaHCO_3 . He was without any significant symptoms or underlying etiology to explain the low HCO_3^- levels. The patient was evaluated by a different nephrologist for a second opinion with repeat basic metabolic panel and arterial blood gas (ABG). These were performed on the same day and resulted in a serum HCO_3^- level of 8 mmol/L in contrast with ABG pH of 7.41 and HCO_3^- of 25 mmol/L. He was advised to discontinue the NaHCO_3 tablets at that time. Further workup was pursued with serum protein electrophoresis (SPEP) and serum immunoelectrophoresis (SIFE) with suspicion that this pseudohypobicarbonatemia may be secondary to an interfering substance. Interestingly, the nephrologist also requested that his plasma from the same day be sent to another facility [using a Beckman Coulter (BC) analyzer], which revealed a normal serum HCO_3^- level of 21 mmol/L. The results of SPEP revealed a monoclonal spike of 0.31 g/dL and SIFE identified the presence of both immunoglobulin M (IgM) and IgA kappa monoclonal proteins, which led to diagnosis of monoclonal gammopathy. Serum free light chain kappa:lambda ratio was elevated at 5.88. Immunoglobulin levels were within normal limits with serum IgM 217 mg/dL (normal 40–274) and IgA 392 mg/dL (normal 82–453). He has since been evaluated by an oncologist who performed a bone marrow biopsy with 5–10% plasma cells with positive Congo red staining. He was diagnosed with amyloid light chain (kappa type) primary amyloidosis with monoclonal gammopathy of undetermined significance. Because cardiac magnetic resonance imaging and positron emission tomography-computed tomography were unremarkable, the plan was for observation alone. Following this workup, he has been having lab work drawn at the second facility (utilizing a BC analyzer) and has had normal serum HCO_3^- levels despite ongoing paraproteinemia.

DISCUSSION

We report a case of erroneously low serum HCO_3^- levels measured using an enzymatic chemistry analyzer. The enzymatic method of measuring of serum HCO_3^- involves the method developed by Forrester *et al.* [10]. This process involves catalyzation of HCO_3^- and phosphoenolpyruvate by phosphoenolpyruvate carboxylase into oxaloacetate and phosphate; oxaloacetate is then reduced to malate with concomitant oxidation of reduced nicotinamide adenine dinucleotide (NADH) [10]. The oxidation of NADH causes a decrease in absorbance of the reaction mixture, which is proportional to the HCO_3^- content

in the sample, and the decrease in absorbance is measured biochromatically.

Our patient was diagnosed with primary amyloidosis with IgM and IgA kappa monoclonal proteins that we believe interfered with the assay, leading to the misdiagnosis of HAGMA. Paraproteins have been reported to cause interference with multiple laboratory test results [11]. Per our review of the literature, only two such cases of paraproteins causing spuriously low serum HCO_3^- levels have previously been reported [6, 9], making this a rare entity. Paraproteins in this case may have resulted in artifactual error by either direct interaction with the assay reagents, binding of paraproteins to an assay reagent or turbidity caused by precipitation of the patient's monoclonal proteins. Unfortunately, because the patient and hematology team decided on supportive care alone, we were unable to directly show that treatment of his paraproteinemia reversed the pseudohypobicarbonatemia seen with the SV analyzer.

What makes this case more intriguing is that both the chemistry analyzers used in this case employ a similar enzymatic method of serum HCO_3^- measurement. At the first facility, the SV analyzer was used, which resulted in erroneously low readings of serum HCO_3^- levels. The BC analyzer was subsequently used, which revealed normal serum HCO_3^- levels. With the same underlying principle of detecting serum HCO_3^- levels, we believe that the difference is likely due to the different wavelengths used by these two analyzers. The SV uses wavelengths of 450 nm (primary) and 700 nm (secondary) to measure the decrease in absorbance of the reaction mixture, while the BC analyzer uses 380 and 410 nm. It is possible that due to this key difference, the SV analyzer may be more susceptible to paraprotein interference. Of note, the BC analyzer datasheet makes no mention of possible interference with paraproteins. The SV analyzer datasheet makes no mention of paraproteins but does state that IgG in amounts <5 g/dL will not interfere with the enzymatic method. The two immunoglobulin levels measured, IgM and IgA, were found in considerably reduced amounts of 217 and 392 mg/dL, respectively.

CONCLUSION

In conclusion, although seemingly rare, factitious measurements of serum HCO_3^- levels can occur in the setting of undiagnosed paraproteinemia. This is clinically relevant, not only for accurate diagnosis of acid-base disorders, but also due to the cost and risk of complications from unnecessary testing that would ensue and the potential side effects that the patient can be exposed to from intravenous and/or oral NaHCO_3 therapy [12]. Our case highlights the importance of being aware of this phenomenon of pseudohypobicarbonatemia that can occur with certain chemical analyzers in the setting of paraproteinemia.

FUNDING

None declared.

DATA AVAILABILITY STATEMENT

No research data available.

CONFLICT OF INTEREST STATEMENT

None declared.

PATIENT CONSENT

Obtained and available upon request.

REFERENCES

1. Centor RM. Serum total carbon dioxide. In: Walker HK, Hall WD, Hurst JW (eds). *Clinical Methods: The History, Physical, and Laboratory Examinations*. 3rd edn. Boston: Butterworths, 1990: 888–889
2. Schindler EI, Brown SM, Scott MG. Electrolytes and blood gases. In: Rifai N, Horvath AR, Wittwer CT (eds). *Tietz Textbook of Clinical Chemistry and Molecular Diagnostics*. 6th edn. St Louis: Elsevier, 2017: 604–625
3. Abott Point of Care. *i-STAT Chem8+ Cartridge Package Insert*. Abbott Park, IL: Abbott Laboratories, 2012
4. Lustgarten JA, Creno RJ, Byrd CG et al. Evaluation of contemporary methods for serum CO₂. *Clin Chem* 1976; **22**: 374–378
5. Kaufman RA. Use of NADPH and NADH analogs in the measurement of enzyme activities and metabolites. U.S. Patent No. 5,801,006. Washington, DC: U.S. Patent and Trademark Office, 1998
6. Goldwasser P, Manjappa NG, Luhrs CA et al. Pseudohypobicarbonatemia caused by an endogenous assay interferent: a new entity. *Am J Kidney Dis* 2011; **58**: 617–620
7. Rifkin SI, Shaub B. Factitious hypobicarbonatemia associated with profound hyperlipidemia. *Ren Fail* 2014; **36**: 1155–1157
8. Carag C, Baxi PV, Behara V et al. Pseudo-anion gap metabolic acidosis from severe hypertriglyceridemia corrected by plasma exchange. *Clin Nephrol* 2019; **92**: 258–262
9. Lazzouni I, Cornec E, Meskar A et al. [Pseudohypobicarbonatemia in a patient with a kappa IgA monoclonal gammopathy]. *Ann Biol Clin (Paris)* 2014; **72**: 599–601
10. Forrester RL, Wataji LJ, Silverman DA et al. Enzymatic method for determination of CO₂ in serum. *Clin Chem* 1976; **22**: 243–245
11. Roy V. Artifactual laboratory abnormalities in patients with paraproteinemia. *South Med J* 2009; **102**: 167–170
12. Sabatini S, Kurtzman NA. Bicarbonate therapy in severe metabolic acidosis. *J Am Soc Nephrol* 2009; **20**: 692–695