AJKD
Teaching Case

Metabolic Acidosis or Respiratory Alkalosis? Evaluation of a Low Plasma Bicarbonate Using the Urine Anion Gap

Daniel Batlle, MD,[1] Jamie Chin-Theodorou, MD,[1] and Bryan M. Tucker, DO, MS[2]

Teaching Cases focus on interpretation of pathology findings, laboratory tests, or imaging studies to educate readers on the diagnosis or treatment of a clinical problem.

Hypobicarbonatemia, or a reduced bicarbonate concentration in plasma, is a finding seen in 3 acid-base disorders: metabolic acidosis, chronic respiratory alkalosis and mixed metabolic acidosis and chronic respiratory alkalosis. Hypobicarbonatemia due to chronic respiratory alkalosis is often misdiagnosed as a metabolic acidosis and mistreated with the administration of alkali therapy. Proper diagnosis of the cause of hypobicarbonatemia requires integration of the laboratory values, arterial blood gas, and clinical history. The information derived from the urinary response to the prevailing acid-base disorder is useful to arrive at the correct diagnosis. We discuss the use of urine anion gap, as a surrogate marker of urine ammonium excretion, in the evaluation of a patient with low plasma bicarbonate concentration to differentiate between metabolic acidosis and chronic respiratory alkalosis. The interpretation and limitations of urine acid-base indexes at bedside (urine pH, urine bicarbonate, and urine anion gap) to evaluate urine acidification are discussed.
Am J Kidney Dis. 70(3):440-444.

INDEX WORDS: Urine anion gap (UAG); acid-base disorders; hypobicarbonatemia; arterial blood gas (ABG); urine pH; urinary ammonium; urine acidification; chronic respiratory alkalosis; renal excretion; nephrology.

INTRODUCTION

A complete evaluation of patients with low plasma bicarbonate (HCO_3^-) concentrations should ideally include an assessment of urine acid excretion, particularly its main component, ammonium (NH_4^+). Such an evaluation would reveal that urinary ammonium excretion is increased, as is the case with hypobicarbonatemia due to metabolic acidosis, or decreased, as is the case with hypobicarbonatemia due to chronic respiratory alkalosis (CRA).[1-3] In the absence of information for ammonium excretion, which is rarely done in most clinical laboratories, the urine anion gap (UAG), also referred as the urinary net charge gap or urine cation gap, can direct the clinician to the proper diagnosis.[3-5] In this article, we discuss a case of low plasma bicarbonate concentration and the use of UAG, even before acquiring an arterial blood gas (ABG), to help arrive at a correct diagnosis of the cause of hypobicarbonatemia. When one considers the invasiveness of the ABG, this approach has practical value but is not meant to replace the ABG. The use of UAG as a practical tool in the evaluation of the kidney's response in terms of ammonium excretion to a low plasma bicarbonate concentration and how it differs in metabolic acidosis and CRA is discussed.

CASE PRESENTATION

Clinical History and Initial Laboratory Data

An 82-year-old woman presented to the hospital after a mechanical fall and was found to have a stroke as a result of a right occipital hemorrhage. Her medical history was significant for multiple strokes, dementia, hypertension, and atrial fibrillation. She was admitted to the intensive care unit for monitoring and later was transferred to the neurology floor. She remained stable and repeated imaging demonstrated a resolving brain hemorrhage.

On physical examination, the patient was arousable but did not follow commands. She was breathing comfortably on room air but with deep inspirations noted. Other pertinent findings included a cachectic body habitus with clear lung fields. Laboratory tests showed the following values: sodium (Na^+), 142 mEq/L; potassium (K^+), 3.9 mEq/L; chloride (Cl^-), 118 mEq/L; total carbon dioxide, 16 mEq/L; plasma anion gap, 11.9 mEq/L; and plasma creatinine, 0.88 mg/dL (corresponding to estimated glomerular filtration rate of 75 mL/min/1.73 m^2 by the MDRD equation). A nephrology consult was requested for evaluation of a presumed metabolic acidosis. Urine electrolytes showed pH of 6; sodium, 35 mEq/L; potassium, 93 mEq/L; and chloride, 66 mEq/L; with UAG of 62 mEq/L. No ketones or glucose were detected in urine, which had specific gravity of 1.020. An ABG showed blood pH of 7.40; P_{CO_2}, 24 mm Hg; P_{O_2}, 89 mm Hg; and bicarbonate, 14.4 mEq/L.

From the [1]Division of Nephrology & Hypertension, Department of Medicine, The Feinberg School of Medicine, Northwestern University, Chicago, IL; and [2]Section of Nephrology, Department of Medicine, Yale University School of Medicine, New Haven, CT.

Received December 27, 2016. Accepted in revised form April 14, 2017. Originally published online June 13, 2017.

Address correspondence to Daniel Batlle, MD, Division of Nephrology & Hypertension, Department of Medicine, The Feinberg School of Medicine, Searle Building Room 10-511, 320 E Superior, Northwestern University, Chicago, IL 60611. E-mail: d-batlle@northwestern.edu

0272-6386
http://dx.doi.org/10.1053/j.ajkd.2017.04.017

Additional Investigations

In the following days, 2 further ABG measurements were performed. The first gave the following values: pH of 7.44; P_{CO_2}, 23 mm Hg; and bicarbonate, 15.1 mEq/L. The second gave pH of 7.47; P_{CO_2}, 24 mm Hg; and bicarbonate, 18 mEq/L.

Diagnosis

This patient's acid-base disturbance is a primary chronic respiratory alkalosis attributable to hyperventilation from central nervous system involvement secondary to strokes. A mixed CRA and metabolic acidosis cannot be ruled out because the initial ABG was consistent with both a pure CRA with complete renal compensation and a mixed CRA and metabolic acidosis. Because a clinical cause for metabolic acidosis was lacking in this patient, the diagnosis of primary CRA with adequate metabolic (renal) compensation was made, consistent with the additional ABG measurement.

Clinical Follow-up

The recommendation of the nephrology consultant to the primary service was to avoid administration of sodium bicarbonate. The rationale for the consultant's recommendation was that blood pH was in the upper range of normal or even increased as a result of CRA and rather than the presumed metabolic acidosis, the patient had a CRA.

DISCUSSION

This teaching case is presented to illustrate that even before performing an ABG, one can begin to evaluate the acid-base disturbance causing the low plasma bicarbonate concentration using UAG as a marker of urine ammonium excretion. Traditionally, UAG is used to separate a hyperchloremic metabolic acidosis of gastrointestinal origin from distal renal tubular acidosis (dRTA).[4] When used as a surrogate marker for urine ammonium, UAG decreases and becomes negative if the increase in excretion of ammonium (the cation) is robust as part of the normal renal adaptive response to the metabolic acidosis of extrarenal origin, such as diarrhea.[4] This is in sharp contrast to situations in which ammonium excretion is decreased despite metabolic acidosis, such as occurs in dRTA or advanced chronic kidney disease (CKD).[3,4] In this case, the diagnosis of CRA as the cause of the low plasma bicarbonate concentration was suspected before ABG evaluation because the patient had hyperventilation on physical examination and the UAG was positive. Moreover, there were no clinical features to suspect metabolic acidosis caused by dRTA and the patient did not have CKD to explain the low bicarbonate concentration and positive UAG. The diagnosis of CRA was confirmed by the ABG and was attributed to central nervous system involvement from a recent stroke, a well-known cause of chronic hyperventilation.[6] In CRA, the renal adaptation involves suppression of ammonium excretion and decreasing bicarbonate reabsorption.[1,2,7] This results in a net reduction in acid excretion and decrease in plasma bicarbonate concentration that is compensatory because it helps attenuate the increase in blood pH.[1-3] The compensatory renal response is so efficient in lowering plasma bicarbonate concentrations that blood pH is close to normal. Because measurement of urinary ammonium excretion is usually not performed in the clinical setting, we emphasize that the UAG can be helpful in the initial evaluation of the cause of a low plasma bicarbonate concentration.

Before discussing UAG as a surrogate marker for urine ammonium content, we first discuss 2 other bedside parameters that are also in use to assess the kidney response to a low plasma bicarbonate concentration: urine pH and urine bicarbonate excretion. Depending on acid-base status and diet, the range of urine pH varies widely from 4.5 to 8.0. Urine pH measures free hydrogen ions (H^+) and this in turn depends on urine buffer concentrations. pH $<$ 6.5 suggests that the urine contains negligible amount of bicarbonate. Urine pH can be affected by various factors (Box 1).[8-11] In the setting of chronic metabolic acidosis, distal H^+ excretion increases, yet this may or may not be reflected in a low urine pH. For example, in chronic metabolic acidosis, ammonia (NH_3) production increases to such an extent that secreted H^+ is almost completely buffered.[12] In this situation, free H^+ concentration is very low[12] and therefore urine pH may not decrease below 5.5 (despite enhanced distal H^+ secretion) due to its buffering by ammonia. Therefore, pH $>$ 5.5 in the setting of chronic metabolic acidosis does not necessarily suggest a defect in H^+ secretion. This concept of nonacidic urine, as reflected by urine pH $>$ 5.5 in the setting of increased net acid excretion, is a reason why urine pH should not be heavily relied on when determining the renal capacity to excrete acid.[8] Other than the presence of urinary buffers, urine pH can be affected by very low urinary sodium concentrations. In states of avid renal sodium reabsorption, urine pH may be relatively

Box 1. Factors Affecting Urine pH

Situations in which urine pH cannot be <5.5
- Bicarbonaturia of any cause
- Metabolic alkalosis
- Impaired distal H^+ secretion (ie, distal RTA)
- Inadequate distal Na^+ delivery (ie, hepatorenal syndrome)

Situations in which urine pH should be <5.5
- Acute metabolic acidosis[a]
- Lack of urinary ammonia buffer; ie, patients with hyperkalemia and aldosterone deficiency (type 4 RTA)
- High acid load (dietary acid such as normal- to high-protein diet) or after an acid load (ammonium chloride test)
- Provocative tests such as furosemide, furosemide + fludrohydrocortisone, or sodium sulfate

Abbreviations: H^+, hydrogen ion; Na^+, sodium ion; RTA, renal tubular acidosis.

[a]Chronic metabolic acidosis can present with variable urine pH because it depends on urinary buffers present.