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

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Abstract

Hypobicarbonatemia or a reduced level of bicarbonate in plasma is a finding seen in three 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, the arterial blood gas (ABG) and the 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 the urine anion gap (UAG), as a surrogate marker of urine ammonium, in the evaluation of a patient with low plasma bicarbonate to differentiate between metabolic acidosis and chronic respiratory alkalosis. The interpretation and limitations of urine acid-base indices at bedside (urine pH, urine bicarbonate and urine anion gap) to evaluate urine acidification are discussed.

Keywords

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^-) 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

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is the case with hypobicarbonatemia due to metabolic acidosis, or decreased, as is the case with hypobicarbonatemia due to chronic respiratory alkalosis¹⁻³. In the absence of information on ammonium excretion, which is rarely done in most clinical laboratories, the urine anion gap (UAG), also referred as the urinary net charge gap or the urine cation gap, can direct the clinician to the proper diagnosis³⁻⁵. In this article, we discuss a case of low plasma bicarbonate and the use of the urine anion gap even prior to 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 it is not meant to replace the ABG. The use of the UAG as a practical tool in the evaluation of the kidney's response in terms of ammonium excretion to a low plasma bicarbonate and how it differs in metabolic acidosis and chronic respiratory alkalosis 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 past 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 repeat imaging demonstrated a resolving brain hemorrhage.

On physical exam, 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 CO_2 16 mEq/L; plasma anion gap 11.9 mEq/L and plasma creatinine 0.88 mg/dl (corresponding to an estimated glomerular filtration rate of ** by the *** equation). A nephrology consult was requested for evaluation of a presumed metabolic acidosis. Urine electrolytes showed a pH of 6, sodium 35 mEq/L; potassium 93 mEq/L; chloride 66 mEq/L with a urine anion gap (UAG) of 62 mEq/L. No ketones and glucose were detected in the urine, which had a specific gravity of 1.020. An arterial blood gas showed a blood pH of 7.40, pCO_2 24 mmHg, pO_2 89 mmHg and bicarbonate 14.4 mEq/L.

Additional Investigations

In the following days, 2 further ABG measurements were performed. The first gave a pH: 7.44, pCO_2 : 23 mmHg, bicarbonate : 15.1 mEq/L. The second gave pH: 7.47, pCO_2 : 24 mmHg, 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 since the initial ABG was consistent with both a pure CRA with complete renal compensation and a mixed CRA and metabolic acidosis. Since 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 the administration of sodium bicarbonate. The rationale for the consultant's recommendation was that the blood pH was in the upper range of normal or even increased as a result of CRA and that rather than the presumed metabolic acidosis, the patient actually had a CRA.

Discussion

This teaching case is presented to illustrate that even prior to obtaining the ABG, one can begin to evaluate the acid-base disturbance causing the low plasma bicarbonate using the UAG as a marker of urine ammonium concentration. Traditionally, the 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, the UAG decreases and actually 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 diarrhea⁴. This is in sharp contrast to situations where ammonium excretion is decreased despite metabolic acidosis, such as occurs in distal renal tubular acidosis or advanced chronic kidney disease (CKD)^{3,4}. In this case, the diagnosis of CRA as the cause of the low plasma bicarbonate was suspected prior to ABG evaluation because the patient had hyperventilation on physical exam 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 and the positive UAG. The diagnosis of CRA was confirmed by the ABG and was attributed to CNS involvement from a recent stroke, a well-known cause of chronic hyperventilation⁶. 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 a fall in plasma bicarbonate that is compensatory, as it helps to attenuate the rise in blood pH¹⁻³. In fact, the compensatory renal response is so efficient in lowering plasma bicarbonate, that the blood pH is close to normal. Since measurement of urinary ammonium is usually not performed in the clinical setting, here we emphasize that the UAG can be helpful in the initial evaluation of the cause of a low plasma bicarbonate.

Prior to discussing the UAG as a surrogate marker for urine ammonium content we will first discuss two other bedside parameters that are also in use to assess the kidney response to a low plasma bicarbonate: the urine pH and the urine bicarbonate. Depending on the 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 the urine buffer concentrations. A pH below 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 buffered¹². In this situation, the free H^+ concentration is

actually very low¹² and therefore pH of the urine may not fall below 5.5 (despite enhanced distal secretion of H⁺) due to its buffering by ammonia. Therefore, a pH greater than 5.5 in the setting of a chronic metabolic acidosis does not necessarily suggest a defect in H⁺ secretion. This concept of a nonacidic urine, as reflected by a urine pH higher than 5.5 in the setting of increased net acid excretion, is a reason why urine pH should not be heavily relied upon when determining the renal capacity to excrete acid⁸. Other than the presence of urinary buffers, urine pH can be affected by very low levels of urinary sodium. In states of avid renal sodium reabsorption the urine pH may be relatively alkaline. For example, low distal sodium delivery as in volume depletion or liver cirrhosis limits optimal distal H⁺ secretion^{13,14}. In these conditions, there is less sodium ion absorbed via eNaC (the epithelial Na⁺ channel) resulting in a reduction of the trans-epithelial negative gradient required for optimal H⁺ secretion¹⁵. Increasing distal sodium delivery through saline infusion or furosemide administration lowers the urine pH by facilitating delivery and thus sodium ion transport via eNaC¹⁵.

Patients with distal RTA are unable to acidify their urine to less than 5.5, even with an acute acid load or with severe spontaneous metabolic acidosis^{15,16}. In proximal RTA, urine pH is high when plasma bicarbonate is normal but falls near maximally and remains low when plasma bicarbonate falls below a critical level¹⁶. Lastly, hyporeninemic hypoaldosteronism (type IV RTA) causes hyperkalemia, which leads to inhibition of ammonia production and excretion. In this situation, the urine pH is low despite a reduction in net acid excretion because of a lack of ammonia buffer¹⁷. This is another situation where low urine pH could mislead by giving the impression that distal acidification is normal, when in reality it is markedly diminished. In the setting of chronic respiratory alkalosis, the kidneys excrete more bicarbonate and urine pH increases transiently until a new steady state is reached while plasma bicarbonate has declined in compensation for the alkalemia⁷.

As in the calculation of plasma anion gap, bicarbonate should be a part of the UAG calculation (Formula #1). When bicarbonate in the urine is high, it can contribute significantly to the UAG; therefore it is important to rule out bicarbonaturia. However, if urine pH is < 6.5, urine bicarbonate does not need to be included as it can be considered negligible as discussed above. Our patient had a urine pH of 6.0 and therefore we can assume that the concentration of bicarbonate present is insignificant and without any impact on the UAG calculation. Therefore, formula #2 is the one used to calculate the UAG and under most circumstances, the urine bicarbonate can be omitted from the calculation.

$$\text{Formula \# 1: UAG} = ([\text{Na}^+] + [\text{K}^+]) - ([\text{Cl}^-] + [\text{HCO}_3^-])$$

$$\text{Formula \#2: UAG} = [\text{Na}^+] + [\text{K}^+] - [\text{Cl}^-]$$

The principle for the use of the UAG is the same to that of the plasma anion gap, namely, that the sum of all anions must equal the sum of all cations⁴ (Formula #3). The unmeasured anions (UA) in the urine include sulfate, phosphate, and organic anions. Unmeasured cations (UC) in urine—or at least ones that are not routinely measured—include NH₄⁺, Ca²⁺, and Mg²⁺. Including anions (Cl⁻, HCO₃⁻) and cations (Na⁺, K⁺) routinely measured, it follows that:

$$\text{Formula \#3: } [\text{Cl}^-] + [\text{HCO}_3^-] + \text{UA} = [\text{Na}^+] + [\text{K}^+] + \text{UC}$$

This formula can be expressed as follows:

$$\text{Formula \#4: UA} - \text{UC} = ([\text{Na}^+] + [\text{K}^+]) - ([\text{Cl}^-] + [\text{HCO}_3^-]) = \text{UAG}$$

$$\text{Formula \#5: UAG} = \text{UA} - \text{UC}$$

It is formula #5 that best allows us to appreciate how UAG can be affected by changing either UA or UC. With this formula one can easily visualize the impact of an acid-base-mediated change of ammonium, the main unmeasured cation in the urine. If ammonium increases, then the UAG decreases and becomes negative. If ammonium does not increase appropriately then the UAG is increased and remains positive. With this principle, and since ammonium is the predominant cation in metabolic acidosis, the UAG can be used to indirectly estimate ammonium excretion in the appropriate clinical situations⁴. A normal or expected response to systemic acidosis is a negative UAG (representing the expected increase in ammonium excretion) (Figure 1).

An example of this can be seen in diarrhea-induced hyperchloremic metabolic acidosis, where the loss of bicarbonate ions in the stool results in a compensatory increase in ammonia production and acid excretion by the kidney⁴ (Figure 1). When there is impaired ammonium excretion, a positive UAG is present as reported consistently in patients with dRTA. This is the one situation where there are no reported exceptions in the literature of both acquired⁴ and hereditary¹⁸ forms of distal RTA. The UAG is always positive and is part of the initial diagnostic evaluation for distal RTA.

By using the UAG, one is assuming the major unmeasured cation is ammonium and that other unmeasured anions or cations are not concurrently altered to any major extent. The UAG can change with any substantial changes in unmeasured anion as lactate and ketoanions. For instance, in patients with diabetic ketoacidosis there is an increase in ammonium but also an increase in excretion of ketoanions, with opposing effects on the UAG (Formula 5). Therefore, the UAG cannot be used to predict the ammonium content in this situation. Another potential variable influencing UAG is diet¹⁹. However, the changes elicited by dietary protein, which increases acid production, on the UAG may not be large enough to have a clinically relevant effect. CKD is associated with a hyperchloremic metabolic acidosis due to decreased production and excretion of ammonium. Because patients with CKD already have impaired acid excretion, measuring UAG in this population is unnecessary as it always yields a positive value despite metabolic acidosis.

Although the UAG clearly reflects urine ammonium excretion in hyperchloremic metabolic acidosis, it is not a precise diagnostic index. The most important requirement for its use is that the patient needs to have a stimulus for ammonium excretion (or a stimulus to decrease ammonium excretion as in our patient with chronic respiratory alkalosis). Evaluating the UAG in patients who are not acidotic usually results in a positive UAG, but results are meaningless due to the lack of correlation between ammonium and the UAG in non-acidotic states. It is therefore of paramount importance to understand the limitations to the UAG and have a clear expectation of when it is a valuable tool. Specifically, it is a useful bedside index of ammonium excretion in two clinical situations: In the setting of a hyperchloremic metabolic acidosis it aids in distinguishing between certain etiologies: diarrheal states from distal RTA (Box 2); in CRA, the UAG can help in evaluating the cause of a low plasma

bicarbonate, as our teaching case illustrates. CRA, like metabolic acidosis, presents with hyperchloremia and hypobicarbonatemia^{1,2}. As a result, clinicians might mistakenly diagnose a patient with CRA as having metabolic acidosis, especially when blood pH and blood PCO₂ are unavailable. A positive UAG along with hyperchloremia and hypobicarbonatemia suggests either CRA or dRTA³. In CRA, the UAG is increased (positive) on account of suppressed ammonium excretion, which is compensatory response to chronic alkalemia. Because dRTA is relatively rare and CRA is frequently observed in hospitalized patients, the UAG helps to distinguish metabolic acidosis from CRA in the initial evaluation of hypocarbonatemia.

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Box 1

Factors affecting urine pH

Situations where urine pH cannot be lower than 5.5

- Bicarbonaturia of any cause
- Metabolic Alkalosis
- Impaired distal H^+ secretion (i.e. distal RTA)
- Inadequate distal Na^+ delivery (i.e. hepatorenal syndrome)

Situations where urine pH should be lower than 5.5

- Acute Metabolic acidosis *
- Lack of urinary ammonia buffer i.e. 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 + fludro-hydrocortisone or sodium sulfate

* Chronic metabolic acidosis can present with variable urine pH as it depends on urinary buffers present

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

Box 2

Summary of Teaching Points

- Chronic respiratory alkalosis presents with hyperchloremia and hypobicarbonatemia resembling a metabolic acidosis unless the ABG is available.
- In chronic respiratory alkalosis there is a reduction in NH_4^+ excretion by the kidneys as part of the renal compensatory response that lowers the plasma HCO_3^- and attenuates alkalemia.
- The UAG is a surrogate marker of urine NH_4^+ in the context of a low plasma levels of HCO_3^- .
- The UAG is increased (positive) in chronic respiratory alkalosis and dRTA, but decreased (negative) in hyperchloremic metabolic acidosis due to HCO_3^- loss through the gastrointestinal tract such as in diarrheal states.

Abbreviations: ABG, arterial blood gas; UAG, urine anion gap; NH_4^+ ammonium ion; NH_3 , ammonia; dRTA, distal renal tubular acidosis

Figure 1.

Urinary ammonium (NH_4^+) in relation to the urinary anion gap (UAG) for 38 patients with different types of distal renal tubular acidosis (blue circles); seven apparently healthy individuals receiving ammonium chloride (green circles); and eight patients with hyperchloremic metabolic acidosis associated with diarrhea (red triangles). Adapted from Battle et al⁴ with permission of the Massachusetts Medical Society.