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Hyperchloremic Acidosis in the Critically Ill: One of the Strong-Ion Acidoses?

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Decreases in plasma bicarbonate are associated with hyperchloremic acidosis and lactic acidosis. According to the Stewart approach to acid-base physiology, the strong-ion difference regulates plasma bicarbonate, with chloride and lactate being the only strong anions routinely measured in clinical chemistry. We hypothesized that the plasma strong-ion difference, both with and without lactate, would have a stronger association with plasma bicarbonate than plasma chloride alone would have with bicarbonate. We used plasma acid-base data from 300 critically ill patients. The correlation with bicarbonate became progressively weaker (P < 0.001): all measured strong ions, r = 0.60; measured strong ions without lactate, r = 0.42; chloride alone, r = −0.27. In a subgroup of 26 patients with traditional hyperchloremic acidosis (base excess < −2 mmol/L and anion gap < 17 mmol/L), the measured strong-ion difference (without lactate) had a stronger correlation (P < 0.001) with bicarbonate than chloride had: r = 0.85 versus r = −0.60. We conclude that hyperchloremic acidosis and lactic acidosis are strong-ion acidoses. Hyperchloremia should be viewed relative to the plasma strong cations. A practical conclusion is that both managing and preventing acid-base disorders with IV fluid therapy involves manipulating each of the plasma strong ions, particularly sodium and chloride.

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Since the 1920s, clinical chemists have recognized that plasma bicarbonate and plasma chloride often have a reciprocal relationship during both acidosis and alkalosis (1). In anesthesiology, this inverse relationship between chloride and bicarbonate has received renewed attention after several studies of intraoperative acidosis associated with the administration of IV sodium chloride (2,3). This acidosis is often called a “hyperchloremic metabolic acidosis” (4). Decreased plasma chloride is associated with the converse condition, hypochloremic alkalosis, often associated with loop diuretics (5) and loss of gastric fluid (6).

Constable (4) categorized hyperchloremic acidosis as a “strong-ion acidosis,” a category in which strong anions (which also include lactate, ketoacids, sulfates, and others) accumulate relative to the strong cation concentration and reduce the strong ion difference. Following from Constable’s editorial (4) and other work using Stewart’s model of acid-base physiology (7–9), we proposed that plasma bicarbonate would be more closely related to the plasma strong-ion difference than plasma chloride alone. We tested this hypothesis using blood samples from critically ill patients.

METHODS

Data were retrospectively collected from intensive care unit (ICU) records at the Austin Hospital, a tertiary referral hospital affiliated with The University of Melbourne. All samples were taken from arterial lines in patients requiring ICU management. No additional sampling was required. The Austin Health Human Research Ethics Committee waived the need for informed consent.

Data were collected on samples taken at admission to the ICU where the records indicated that simultaneous arterial blood samples were sent for blood gas and general chemistry analysis. Consecutive patients were included if all the clinical chemistry elements required for a detailed analysis were measured. Blood samples were collected in heparinized blood-gas syringes (Rapidlyte; Chiron Diagnostics, East Walpole, MA) and analyzed in the ICU blood gas analyzer (Ciba Corning 865; Ciba Corning Diagnostics, Medfield, MA). The analyzer measured at 37°C. Nursing staff from the ICU, who had been taught to use the machine by support staff, performed analysis. Samples were not stored on ice. We collected data on the pH, partial pressure of carbon dioxide, plasma...
bicarbonate, standard base excess, and plasma sodium, potassium, ionized calcium, and lactate. The machine algorithm calculated the bicarbonate concentration using the Henderson-Hasselbalch equation from the measured pH and partial pressure of carbon dioxide at 37°C. The carbon dioxide solubility coefficient was 0.0307. The measured overall dissociation constant for carbonic acid was 6.105. The machine used the Van Slyke equation to calculate base excess (10).

A further sample was drawn at the same time from the same arterial sampling point using a vacuum technique with lithium heparin tubes or clot-activating tubes (Vacuette, Greiner labortechnik, Kremsmunster, Austria). These samples were sent to the hospital’s core laboratory in the Division of Laboratory Medicine. Plasma and serum underwent a multicomponent analysis (Hitachi 747; Roche Diagnostics, Sydney, Australia). Scientific staff from the hospital clinical chemistry department analyzed the samples. Samples were not stored on ice. We collected data on the plasma or serum concentrations of magnesium, albumin, and phosphate. The magnesium concentration (mmol/L) was multiplied by two to give meq/L.

We calculated the measured strong-ion difference using Figge et al.’s approach (11) of using the strong ions routinely measured in clinical chemistry; this variable is called the apparent strong-ion difference (11) or measured strong-ion difference (12). We used Kellum et al.’s (13) modification by including lactate measurements:

\[
\text{Measured strong-ion difference, meq/L} = [Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}] - [Cl^-] - [\text{lactate}^-].
\]

Equation (1)

To exclude the effect of lactic acidosis on bicarbonate we also calculated the measured strong-ion difference without lactate:

\[
\text{Measured strong-ion difference (without lactate), meq/L} = [Na^+] + [K^+] + [Ca^{2+}] + [Mg^{2+}] - [Cl^-].
\]

Equation (2)

A decreased strong-ion difference is associated with greater acidosis and therefore a decrease in the plasma bicarbonate concentration (14). We therefore expected a positive correlation between the measured strong-ion difference and bicarbonate. However, for chloride alone, as acidosis increases, the chloride concentration also increases. Therefore we expected a negative correlation between plasma chloride and bicarbonate. We expected similar relationships between base excess and the strong-ion difference and chloride.

We examined a subgroup with traditional hyperchloremic metabolic acidosis: standard base excess less than –2 mmol/L and anion gap <17 mmol/L, where the anion gap

\[
\text{(mmol/L)} = [Na^+] + [K^+] - [Cl^-] - [HCO_3^-].
\]

Equation (3)

Data collected from patient charts and the hospital computer system were stored on a spreadsheet (Excel; Microsoft, Redmond, WA). We calculated Pearson’s correlation coefficients for correlations between the measured strong-ion difference and bicarbonate, between the measured strong-ion difference (without lactate) and bicarbonate, and between chloride and bicarbonate and the 95% confidence intervals (CIs) for the Pearson coefficients using GraphPad software (GraphPad Software, San Diego, CA). We also calculated the P value for the difference between the Pearson’s coefficients (15) using NCSS 2000 software, assuming that the measured strong-ion difference and chloride were dependent variables (NCSS, Kaysville, UT). To determine the relationship with metabolic acid-base changes we used similar statistical techniques to examine the correlations between the measured strong-ion difference (without lactate) and base excess and between chloride and base excess. In the subgroup with hyperchloremic acidosis, we also compared the measured strong-ion difference (without lactate) and bicarbonate, and chloride and bicarbonate.

RESULTS

We analyzed the biochemistry results for 300 samples taken from 300 patients at the time of admission to the ICU. These patients, admitted during 2001 and 2002, had a broad spectrum of acid-base conditions, ranging from severe acidemia, pH 6.93, to severe alkalemia, pH 7.61 (Table 1).
Comparisons between bicarbonate and the measured strong-ion difference (Figure 1), the measured strong-ion difference without lactate, and chloride showed that the correlation strength decreased progressively. The measured strong-ion difference had a moderate (r = 0.60; 95% CI, 0.53 to 0.67; P < 0.001) positive association with bicarbonate. The measured strong-ion difference (without lactate) had a moderate, but weaker (r = 0.43; 95% CI, 0.33 to 0.52; P < 0.001), positive association with bicarbonate. Chloride, however, had only a mild (r = 0.27; 95% CI, −0.37 to −0.16; P < 0.001) negative association with bicarbonate (r = −0.40), as did chloride (r = −0.28).

There were 26 patients in the subgroup with traditional hyperchloremic metabolic acidosis: standard base excess less than −2 mmol/L and anion gap <17 mmol/L. The measured strong-ion difference (without lactate) had a strong correlation with bicarbonate (r = 0.85; 95% CI, 0.68 to 0.93; P < 0.001). Chloride had a statistically weaker (P < 0.001) moderate negative association with bicarbonate (r = −0.60; 95% CI, −0.28 to −0.80; P < 0.001).

**DISCUSSION**

The traditional thinking has been that plasma bicarbonate is inversely related to chloride, leading to the terms “hyperchloremic acidosis” (4) and “hypo-chloremic alkalosis” (5). However, consistent with our hypothesis, we found that in 300 critically ill patients with a broad range of acid-base disorders, plasma bicarbonate had a stronger association with the strong-ion difference of plasma ions routinely measured in clinical chemistry than with chloride alone. The association was strongest when both chloride and lactate anions were used to calculate the measured strong-ion difference. When the lactate effect was removed, the measured strong-ion difference, with only chloride anions, had a stronger association with bicarbonate than chloride alone had with bicarbonate. This association was particularly strong in a subgroup with typical hyperchloremic metabolic acidosis. Although association does not necessarily equal causation, we feel, however, that this finding provides some support for the Stewart approach to acid-base physiology and disorders (7, 8, 14), particularly the proposition that plasma bicarbonate is controlled, in part, by the strong-ion difference (9).

In Stewart’s approach (7), the three independent factors in acid-base status are the partial pressure of carbon dioxide, the strong-ion difference, and the total concentration of weak acids. The overall status will depend on the combined effect of all the components of these three factors. In critically ill patients, both the strong-ion difference and the total weak acid concentration are likely to include both measured and unmeasured components. We focused on one group (measured plasma strong ions) of the many elements that influence acid-base status. Other factors will be important in determining the plasma concentration of bicarbonate (7, 9) and will reduce the strength of association tested in this study. In this study, however, these factors should have had identical effects on both the association between the measured strong-ion difference and bicarbonate and the weaker association between chloride and bicarbonate. Other factors affecting plasma bicarbonate concentration include the partial pressure of carbon dioxide, although the base-excess correlation was similar, and the concentration of weak acids such as albumin and phosphate. As the concentration of the weak acids increases, the plasma bicarbonate would be expected to decrease (4, 7). Plasma bicarbonate may also have been affected by unmeasured strong ions such as acetate and gluconate or unmeasured weak acids such as gelatin (17).
Using the bicarbonate-centered approach, derived from the Henderson-Hasselbalch equation (18), two possible mechanisms for hyperchloremic acidosis are: first, the failure to excrete hydrochloric acid (for example, in renal failure) (18), and second, the dilution of bicarbonate by IV saline (19). In a study of saline dilution, Scheinagrabger et al. (2) administered several liters of 0.9% saline during gynecologic surgery, leading to a large increase in mean plasma chloride (104 to 115 mmol/L) and marked acidemia, with a mean pH of 7.28. This can be seen as a typical hyperchloremic metabolic acidosis, with a mean base excess of –6.7 mmol/L and an anion gap of 11.8 mmol/L (4,20).

Overall, Scheinagrabger et al. found a small increase in plasma sodium: 140 to 142 mmol/L. Therefore, there was also a decreased difference between the major components of the measured strong-ion difference (sodium minus chloride), from around 36 to 27 mmol/L (2,21), which explains the acidosis from the Stewart perspective (4,7). A related, but less obvious, phenomenon is that patients who have normal, or even decreased, plasma chloride and also have decreased plasma sodium can have an acidosis as the result of a decreased strong-ion difference (14,22).

At the other end of the acid-base spectrum is hypochloremic metabolic alkalosis. One cause of this type of alkalosis is loop diuretics, such as furosemide, which lead to greater chloride excretion (5,18). Although a bicarbonate-centered approach uses bicarbonate retention (18) as the mechanism of the alkalosis, the Stewart view is that a loss of chloride due to the diuretic will widen the plasma strong-ion difference, causing the alkalosis (14). Therefore, according to Stewart (7), the measured increase in bicarbonate, though a useful marker of the alkalosis, is only a dependent secondary phenomenon. Further, increased bicarbonate and alkalosis can occur with normal or even increased chloride concentrations in the presence of hypernatremia (14,22).

The findings of this study should be easily accepted by clinicians who use the Stewart acid-base approach. This includes a growing group of anesthesiologists (8,14). But how will it be interpreted by clinicians using the bicarbonate-centered approach? The answer may involve one of the underlying principles of the anion gap: electroneutrality (18), which holds that plasma cannot have an overall electrical charge. Therefore, changes in plasma anions, particularly chloride and bicarbonate, may be partly constrained by the overall plasma cation concentration, particularly the sodium concentration. This constraint appears to be involved in renal electrolyte handling (18). Therefore, according to the bicarbonate-centered approach, during hyponatremia the bicarbonate response to a hydrochloric acid load may be partly constrained by the decreased plasma sodium concentration. Conversely, during hypernatremia, there may be less constraint on the bicarbonate response.

We conclude that hyperchloremic metabolic acidosis, along with lactic acidosis, is a decreased strong-ion difference metabolic acidosis (strong-ion acidosis) (4) and hypochloremic alkalosis is an increased strong-ion difference alkalosis (strong-ion alkalosis). That is, the hyperchloremia and hypochloremia are not necessarily absolute but are relative to the cation concentrations, particularly sodium. Hyperchloremic and lactic acidoses can be viewed as two important types of strong-ion acidosis when using either the Stewart (14) or the bicarbonate-centered (18) approach to acid-base disorders. The Stewart approach, however, allows us to quantify the effects of these acidoses along with other factors affecting overall acid-base status, such as albumin and phosphate (21,23). One practical conclusion is that both managing and preventing acid-base disorders with IV fluid therapy involves manipulating each of the plasma strong ions, particularly sodium and chloride, to optimize the strong-ion difference (4,14).

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