Chloride Ion Is Not the Enemy

To the Editor:

We have read the article by Kimura et al (1) with exceptional interest published in the recent issue of Critical Care Explorations. It should be considered that not all anions and cations are measured in daily clinical practice in seriously ill patients, of the measured ions sodium (Na⁺) represents the highest percentage of cations and chloride (Cl⁻) of anions. The negative charge of Cl⁻ allows it to associate with Na⁺ and be co-responsible for maintaining serum osmolality and Cl⁻ levels are usually regulated by those processes that affect Na⁺, associating the changes of one to the modifications of the other (2), so these ions must be interpreted as a ratio and not as an absolute value. The Na⁺/Cl⁻ ratio can be understood through Stewart's model, which refers to six main disorders of the acid-base state (3) (Fig. 1):

1) Acidosis due to increased Pco₂.
2) Acidosis due to a decrease in strong ion difference apparent: hyperchloremia, hyponatremia (increased water).
3) Acidosis due to increased total weak nonvolatile acids (ATOT): hyperphosphatemia, hyperalbuminemia.
4) Alkalosis due to decrease in Pco₂.
5) Alkalosis due to increased strong ion difference apparent (SIDa): hypocchloremia, hypernatremia (decreased water).
6) Alkalosis due to reduction of ATOT: hypophosphatemia, hypoalbuminemia.

In this approach, the SID is considered as part of the evaluation of metabolic disorders, its increase can be interpreted as metabolic alkalosis and its decrease as metabolic acidosis.

The sodium-chloride difference (Na⁺/Cl⁻) can be used as a substitute for SIDa (R = 0.973) in critically ill patients with a cutoff point less than or equal to 34 mEq/L for the diagnosis of metabolic acidosis and greater than 38 mEq/L for alkalosis metabolic (4).

The chloride/sodium index (Cl⁻/Na⁺) can also replace SIDa (R = 0.959) with a cutoff point greater than 0.77 for metabolic acidosis and less than 0.75 for metabolic alkalosis (5).

In 2015 in our ICU, we used the Na⁺/Cl⁻ difference to predict mortality in patients with septic shock, the cutoff point was less than 31 mEq/L with area under the curve (AUC) 0.83 (95% CI, 0.67–0.93; p = 0.05), sensitivity 87%, specificity 57%; the multivariate analysis showed relative risk 1.59 (95% CI, 1.07–2.36; p = 0.02); and the need for renal replacement therapy (RRT) was not statistically significant (6). Low and high values, compared with normal values (32–34 mEq/L) of the difference Na⁺/Cl⁻ are associated with greater acute kidney injury (AKI) and greater mortality in critically ill patients. These findings suggest that the Na⁺/Cl⁻ difference is a better predictor of ICU outcomes because it evaluates the “Cl⁻ ratio” and not an absolute value (1). Furthermore, the adverse effects of Cl⁻ also depend on the serum change (Δ) through time. In our ICU, we evaluated the chlorine delta (ΔCl⁻) at 24 hours of admission, the cutoff point greater than

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The difference Na⁺/Cl⁻ high is consistently correlated with Cl⁻ low and metabolic alkalosis; on the other hand, the difference Na⁺/Cl⁻ low correlates with Cl⁻ high and metabolic acidosis (8). This occurs because Cl⁻ is reabsorbed and excreted mainly in the proximal tubule in inverse proportion to bicarbonate (HCO₃⁻): if there is hypochloremia, the kidneys retain HCO₃⁻ producing metabolic alkalosis, on the contrary, hyperchloremia leads to a metabolic acidosis due to renal elimination of HCO₃⁻. Over time, we have seen Cl⁻ as a “villain,” but today, we know that patients with hypochloremia (< 96 mEq/L) have a higher risk of AKI than patients with hyperchloremia (> 111 mEq/L) with odds ratio (OR), 2.74; 95% CI, 1.19–6.32; p = 0.02 and OR, 1.26; 95% CI, 0.53–3.01; p = 0.60, respectively. There is also a greater risk (OR, 5.12; 95% CI, 2.56–10.23; p ≤ 0.001) of incomplete renal recovery after RRT compared with patients with hyperchloremia (OR, 2.53; 95% CI, 1.25–5.13; p = 0.01) (9). Hyperchloremia in most patients is iatrogenic and can be avoided, the reason for this is the increased risk of death (OR, 2.50; 95 CI, 2.01–3.12; p ≤ 0.001) that this entails (10).

The understanding of the metabolic alterations caused by dyschloremia is limited when we use the Henderson-Hasselbalch model since it does not consider all the factors that influence acid-base alterations, being HCO₃⁻ a “simple” variable to explain such a complex problem. The principle of electroneutrality (relationship between Na⁺ and Cl⁻) of the Stewart model allows to better evaluate these alterations, but not only that, it could determine what type of solution we should use, for example, if the difference between positive and negative charges of the solution (Hartmann: Na⁺ 131 + K⁺ 5 + Ca⁺ 2 – Cl⁻ 111 = 27) is greater than the standard bicarbonate (HCO₃⁻ std) of the blood gas, the pH and excess base (EB) of the patient will increase, but if the difference between the positive and negative charges of the solution (saline 0.9%: Na⁺ 154/Cl⁻ 154 = 0) is less than the HCO₃⁻ std of the blood gas, the pH and EB will decrease; finally, if the difference between the positive and negative charges of the solution are similar to the HCO₃⁻ std of the blood gas and the patient’s pH and EB will not change (this solution does not appear to exist). The Na⁺/Cl⁻ index could be another option in making decisions regarding what
type of liquid to use, taking into account that the normal \( \frac{Na^+}{Cl^-} \) index in the blood is 1.3 (\( \frac{140}{108} = 1.296 \)), considering that solutions with \( \frac{Na^+}{Cl^-} \) index less than or equal to 1 tend to cause metabolic acidosis and those with \( \frac{Na^+}{Cl^-} \) index greater than or equal to 1 metabolic alkalosis (10). Finally, the adverse effects of dyschloremia can appear with normal or abnormal values of \( Cl^- \) depending on the relationship with \( Na^+ \). Metabolic acidosis or alkalosis can be present even with normal \( Cl^- \) values depending on the amount of \( Na^+ \).

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