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Assessment of Metabolic Acidosis and the use of Albumin-Corrected Plasmatic Anion Gap in Critically Ill Patients

Summary

Understanding the acid-base disorders relies on a structured diagnostic approach, based on Henderson-Hasselbalch's equation. After the diagnosis of metabolic acidosis, the calculation of the plasmatic anion gap (AG) evaluates the excess of unmeasured anions. The reference range is 12±2 mEq/L. However, in the case of complex disorders, we need to correct the calculation with some parameters to get the true AG. Albumin is the most clinically relevant variable to adjust for in the calculation of AG (albumin-corrected anion gap) because it is the most abundant of circulating proteins, and hypoalbuminemia has an alkalizing effect.

Keywords: Acid-base status; Corrected anion gap; Albuminemia

Review Article

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Introduction

Acid-base derangements are among the most common abnormalities seen in critically ill patients [1]. They are generally associated with clinical outcome and disease severity, especially for metabolic acidosis [1,2]. Thus, understanding the nature of these disorders is fundamental to the practice of critical care medicine. The classical approach to acid-base disorders is based on the Henderson-Hasselbalch equation that lies on the law of mass action and the equilibrium in the carbonic acid-bicarbonate buffer system, which is fundamental to the respiratory and renal control of pH. It is mathematically expressed by the following equation:

$$pH = pK + \log_{10} [HCO_3^-]/0.03 \times PaCO_2$$

where pK is the acid dissociation constant, $[HCO_3^-]$ is the bicarbonate concentration in millimoles per liter, 0.03 the solubility of CO_2 in blood and $PaCO_2$ the partial pressure of carbon dioxide in millimeters of mercury [3,4]. A decrease of pH lesser than 7.37, with $[HCO_3^-] < 24$ mmol/L and $PaCO_2 < 40$ mmHg, defines a metabolic acidosis. Thenceforth, it is easy to figure out the limits of this classical approach to acid-base disorders because of the mathematical dependence between bicarbonates and $PaCO_2$. Also, it puts aside the existence of non-bicarbonates buffers and nonvolatile plasmatic weak acids, which are mostly represented by proteins (especially albumin) and phosphate. The next step is to determine the plasmatic anion gap to precise the cause of the metabolic acidosis and its pathophysiological mechanisms.

The plasmatic anion gap (AG)

The chemical principle of electroneutrality defines equality between the sum of positive charges (cations) and negative charges (anions). Only four ions are classically measured at the laboratory: sodium, potassium, chloride and bicarbonates; therefore, the remaining cations and anions can be designated as unmeasured cations (UC) and anions (UA), respectively:

$$[Na^+] + [K^+] + [UC] = [Cl^-] + [HCO_3^-] + [UA]$$

Rearranging the equation, we obtain:

$$[Na^+] + [K^+] - ([Cl^-] + [HCO_3^-]) = [UA] - [UC] = \text{anion gap (AG)}$$

In vivo, the AG should be null, however, because normally the total unmeasured anions exceed the total unmeasured cations, there is an anion gap (Figure 1). Serum potassium is classically not included in the calculation of AG because of its relatively small concentration in the blood compared with that of the other components, but it should be considered when its concentration is high (> 6 mmol/L). The normal value of the AG is 12 ± 2 mEq/L, with wide variations depending on the different studies [5,6]. When potassium concentration is included in the calculation, this value increases to 16 ± 2 mEq/L. These values were based on sodium concentration measured by flame photometry and chloride concentration by a colorimetric method. Nowadays, many clinical laboratories changed their methods of measuring the individual constituents of the anion gap [5,7]. Especially, sodium and chloride methods for measuring concentrations are now more accurate, using new ion-selective electrode technology. As a consequence, the normal mean of AG is lower than reported previously, averaging 7 ± 2 meq/L (potassium not included) [5,7]. However, given the differences in laboratory methods [8,9] clinicians should know the reference range for their own laboratory.

The physiological compensatory response to a metabolic acidosis will be a respiratory alkalosis due to hyperventilation.

This secondary respiratory response is predictable and can be calculated by the following equation: $\Delta PaCO_2 = \Delta [HCO_3^-] \times 1.25$. It can occur within the next 12 or 24 hours. On the other hand, after a respiratory alkalosis, there is a metabolic compensation by a tubular excretion of bicarbonates. In the case of acute respiratory alkalosis, the response will be a decrease of bicarbonates by 2 mmol/L for each $PaCO_2$ decrease of 10 mmHg below 40 mmHg, and for a chronic alkalosis, the decrease of bicarbonates will be 4-5 mmol/L for each $PaCO_2$ decrease of 10 mmHg below 40 mmHg. This complete metabolic compensation will develop slowly, requiring 2 to 5 days for a new steady state level [10]. In some alkalosis situation, we often find an elevation of the AG, due to 3 mechanisms [11]:

a) Increase in lactate production by stimulating glycolysis.

b) Increase in albumin concentration as a result of volume depletion and contraction alkalosis.

c) Increase in the number of anionic charges on albumin.

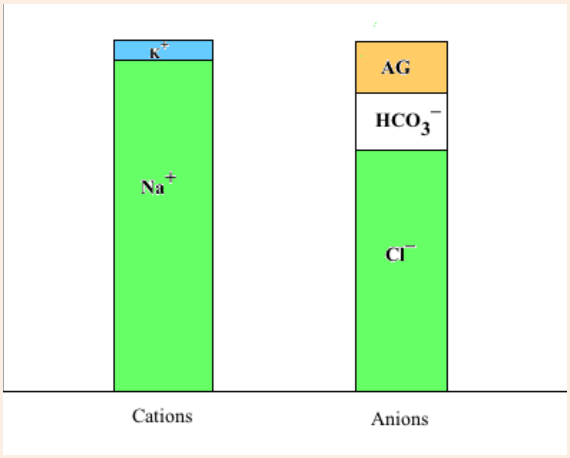

Figure 1: Charge balance in blood plasma.

Metabolic acidosis with normal or high AG

Metabolic acidosis with high AG: The AG is increased if it is more than16 mEq/L, including potassium. When acidosis is linked to the accumulation of a proton combined with an anion not fully metabolized, the accumulation of this unmeasured anion will be responsible for the high AG. To explain this acidosis with high AG, the organic acid responsible for the acidosis has been generated or ingested faster that it can be metabolized or excreted, resulting in a decrease in bicarbonates concentration and accumulation of the sodium linked with this acid in plasma [12]. We define multiple etiologies of metabolic acidosis with high anion gap:

A. Ketoacidosis (diabetic, alcoholic or starvation)

B. Lactic acidosis:

a) L-lactic acidosis: hypoxic (septic shock, carbon monoxide poisoning) or non hypoxic (intoxication: salicylate, methanol, ethylene glycol)

b) D-lactic acidosis in acute mesenteric ischemia [13] or in short bowel syndrome [14].

i. Severe acute kidney injury.

ii. Massive cell lysis (rhabdomyolysis).

iii. Pyroglutamic acid intoxication.

Metabolic acidosis with normal AG: It is always related to hyperchloremia due to an equimolar replacement between bicarbonates and chloride molecules. Hyperchloremic metabolic acidosis is the consequence of a net retention of HCl or a loss of bicarbonates. We can number the following etiologies:

a) Loss of bicarbonates: diarrhea, digestive fistula, and type 2 renal tubular acidosis.

b) Decreased renal acid excretion: type 1 or 4 renal tubular acidosis, and mild acute kidney injury.

c) Exclusive parenteral nutrition, fluid resuscitation with saline, some medications (arginine hydrochloride, cholestyramine, and ammonium chloride).

The albumin-corrected plasmatic anion gap (ACAG)

The value of the AG is widely related to protein negative charges and particularly albumin, which represent 75% of this anionic charge. Human serum albumin is a 67.5 kDa large protein, rich in histidine and negatively charged at physiological pH. Hypoalbuminemia is very common in ICU, with an incidence of 30-40% [15], and has a bad prognostic value. It also has a role in the AG interpretation because hypoalbuminemia has an alkalizing effect. Gabow et al. [16] proposed a correction factor to integrate the albumin concentration in the calculation of the albumin-corrected AG (AcAG). They calculated that a decrease of 2.5 mEq/L of AG should be considered with every 10-g/L fall in albumin concentration. Finally, Figge et al. [17] elaborated the ACAG equation as follow:

AcAG (mEq/L) = AG + 0, 25 x (normal albumin - observed albumin)

Where albumin concentration is in g/L. The value of the correction factor has long been debated because of various population studies. Physiologically, this factor is the net negative charge contributed by the decrease of albumin concentration. The Figge's mathematical model yields a value of 2.3 to 2.5 for the net negative charge contributed by each 10-g/L of albumin concentration (including the charge contributed by bound calcium) as the pH range from 7.20 to 7.50 [18].

Without correction for hypoalbuminemia, more than 50% cases of significant increase in unmeasured anions (> 5 mEq/L) are not detected by the estimated AG. Validation of the AcAG is now well recognized for diagnostic use, particularly in the population of septic shock patients. We demonstrated that AcAG was more accurate to detect the presence of unmeasured anions (> 8 mEq/L) than AG with the area under the ROC curve of 0.995 and 0.865, respectively [19] (Table 1).

Table 1: Area under the receiver operating characteristic curve for each variable to predict the presence of unmeasured anions (strong ion gap > 8 mEq/L).

Variable	AUC	Se (%)	Sp (%)	PPV (%)	NPV (%)
SBE, mEq/L	0.715	70	50	74	45
AG, mEq/L	0.865	35	90	87	41
AcAG, mEq/L	0.995	95	100	100	92

AUC: Area Under ROC Curve; Se: Sensibility; Sp: Specificity; PPV: Positive Predictive Value; NPV: Negative Predictive Value; SBE: Standard Base Excess; AG: Anion Gap; AcAG: Albumin-Corrected Anion Gap

Conclusion

Plasmatic anion gap is an essential tool for the evaluation of metabolic acidosis. The range of normal values of AG for a specific clinical laboratory has to be determined before any calculation. Hypoalbuminemia is a very common finding in intensive care patients, and therefore, the AcAG is the tool needed at the bedside to detect the presence of unmeasured anions because of the lack of accuracy of AG.

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