Use of the $\Delta AG/\Delta HCO_3^-$ Ratio in the Diagnosis of Mixed Acid-Base Disorders

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ABSTRACT

When a strong acid is added to plasma, one expects a quantitative relationship between excess anion gap (ΔAG) and bicarbonate deficit (ΔHCO_3^-) with the $\Delta AG/\Delta HCO_3^-$ ratio close to unity. If true, then this ratio could be used to diagnose mixed acid-base disorders in patients with metabolic acidosis. Although the *mean* ratio in selected patients is close to unity, this ratio also has a wide range, making its use in individual patients problematic. The ratio should therefore be used cautiously in making a diagnosis of mixed acid-base disorders.

The anion gap (AG) is the difference between the concentration of selected positive and negative ions in the plasma. By convention, the AG is usually calculated as $[Na - (Cl + HCO_3^-)]$, ignoring the concentration of potassium; in this commentary, HCO_3^- is also used synonymously for total CO_2 (TCO_2). Because the total concentration of anions and cations in plasma is equal, the AG reflects the difference between the concentration of unmeasured anions and cations.[1] A normal AG primarily reflects the concentration of nonbicarbonate buffers including albumin, phosphate, sulfate, and organic acids. Albumin is the main component of the normal AG with each gram per deciliter contributing 2.5 mEq/L to the gap calculation.[2] This contribution is pH dependent and increases with a rise in ambient pH. The elevated AG seen in metabolic alkalosis is due primarily to an increase in albumin concentration and a lesser extent to alkaline pH.[3] The normal range for the AG varies from 3 to 11 to 8 to 16 mEq/L, depending on the instrument used to measure serum electrolytes, especially chloride.[4] The range, however, is wide, regardless of the instrument used. To evaluate the AG in a patient, it is therefore important to know the normal range in your laboratory and compare the present AG with baseline AG, both corrected for albumin concentration and, if indicated, serum pH. Sometimes the baseline AG has to be estimated on the basis of the albumin concentration at the time of evaluation.

When a strong acid (HA) is added to the plasma, it dissociates to its base (A^-) and H^+ ion. Hydrogen is then neutralized by both bicarbonate and nonbicarbonate buffers present in extra- and intracellular compartments, resulting in a drop in serum bicarbonate (Figure 1). The accumulated A^-, an unmeasured anion, then raises the AG. The resultant excess AG (ΔAG), therefore, serves as a footprint for the accumulation of a strong acid in plasma. ΔAG, of course, often contains more than a single anion. Gabow *et al.*,[5] studying an unselected population with AG metabolic acidosis (AGMA), could not account for 23% (8.7 mEq/L) of the gap. Forni *et al.*,[6] in a group of intensive care unit patients with lactic acidosis, diabetic ketoacidosis (DKA), and acidosis of unknown cause, noted the presence of significant amounts (3 to 5 mEq/L) of Kreb cycle intermediates, including citrate, isocitrate, α-ketoglutarate, and D-lactate. These metabolites accounted for some but not all of the unknown anions.

Metabolic acidosis is due to either loss of bicarbonate or net addition of strong acid(s). In the former, no new anion is added and the AG does not change, resulting in hyperchloremic metabolic acidosis (HCMA). In this disorder, there is a lack of correlation between the ΔAG and ΔHCO_3^-, with the ratio of $\Delta AG/\Delta HCO_3^-$ falling below unity (1.0) and sometimes approaching zero. When a strong acid (HA) is added to plasma either as a result of a decrease in excretion, such as in renal failure, or as a result of addition, such as in DKA or in methanol poisoning, AGMA develops. In this disorder, one expects a direct quantitative relationship between ΔAG and ΔHCO_3^- with a ratio close to unity. If true, then a mixed disturbance is suspected when the ratio deviates from unity. If the ratio is significantly lower than 1, then an underlying HCMA or respiratory alkalosis can be inferred; if greater than 1, then an underlying metabolic alkalosis or respira-

1. **No change in the ratio:**
   a. H^+ space = A^- space (**I**)
   b. Metabolism to CO_2 & H_2O (**II**)
   c. Renal loss as $NH_4^+A^-$ (**III**)
2. **Increase in the ratio:**
   a. H^+ space > A^- space (**I**)
   b. Minimal renal loss of A^- (**III**)
3. **Decrease in the ratio:**
   a. H^+ space < A^- space (**I**)
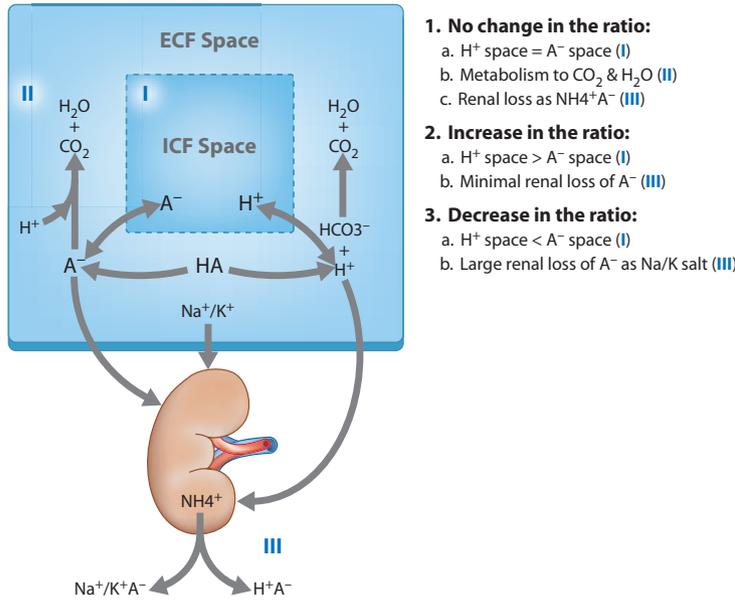   b. Large renal loss of A^- as Na/K salt (**III**)

Figure 1. Factors affecting $\Delta AG/\Delta HCO_3^-$ ratio. I, distribution space for A^- and H^+; II, metabolism of A^-; III, renal handling of A^- and H^+; ECF, extracellular fluid; ICF, intracellular fluid.

tory acidosis may be present. One could also calculate the so-called $\Delta\Delta$—the difference between ΔAG and ΔHCO_3^-. In pure AGMA, the $\Delta\Delta$ would be zero. If the ΔAG is greater than the ΔHCO_3^-, then the $\Delta\Delta$ would be positive. This is plausible only if the initial bicarbonate is higher than normal, reflecting the presence of a hidden metabolic alkalosis or respiratory acidosis. If the $\Delta\Delta$ is a negative number because the ΔAG is less than the ΔHCO_3^-, then the initial bicarbonate must be lower than normal, reflecting the presence of a HCMA or respiratory alkalosis. Use of either the $\Delta AG/\Delta HCO_3^-$ ratio or the $\Delta\Delta$ also requires that A^- and H^+ have a similar distribution space and renal and nonrenal clearance and that the overall contribution of albumin and other nonbicarbonate buffers to the AG remain stable (Figure 1). However, as summarized in Figure 1, the ratio or $\Delta\Delta$ would change if these conditions were not met.

The utility of the $\Delta AG/\Delta HCO_3^-$ ratio is best studied in DKA, in which production of ketoacids is associated with an acute drop in serum bicarbonate and a rise in AG. Patients with DKA often present with vomiting, volume depletion, and/or infection, conditions that could affect acid-base status. Adrogué et al.[7] recently summarized seven studies in patients with DKA and noted that the *mean* rise in AG was similar to the *mean* decrease in bicarbonate, resulting in a $\Delta AG/\Delta HCO_3^-$ ratio close to 1.0. In the largest study involving 242 patients, although the *mean* $\Delta AG/\Delta HCO_3^-$ ratio was close to unity, there was no relationship between ΔAG and ΔHCO_3^-, and the ratio varied from 0 to 2.[8] Similar variations in this ratio have been noted in patients with ESRD.[9] In a carefully done study of 100 admissions for DKA, Paulson,[10] after a careful review of clinical data, selected 20 admissions with simple metabolic acidosis. Slope of regression lines between ΔAG to ΔHCO_3^- in this group and 43 normal control subjects was close to unity but with a wide 95% confidence interval of ± 8 mEq/L. Given this wide interval, two conclusions can be drawn: (*1*) The AG in itself is often a poor predictor of severity of metabolic acidosis, and (*2*) the $\Delta AG/\Delta HCO_3^-$ ratio should be used cautiously in diagnosing a mixed acid-base disturbances.

When this ratio was further evaluated in light of volume status (blood urea nitrogen [BUN] used as a surrogate for volume status), there was a direct relationship between BUN and this ratio as well as among BUN, serum albumin, and the AG.[8,10] This relationship is primarily due to the effect of volume status on renal clearance of keto-anions. Lower renal clearance of keto-anion in hypovolemia also explains two other observations: (*1*) That volume expansion is associated with the development of HCMA,[8,11] and (*2*) that patients with higher $\Delta AG/\Delta HCO_3^-$ ratios on admission have a more rapid rise in bicarbonate generated by metabolism of keto-anions.[8] In summary, the expected stoichiometric relationship seems true only of the *mean* data, with a wide range for individual patients. In addition, volume depletion, by changing the renal excretion of keto-anions, has a major impact on this ratio.

Given this complex relationship, how should the $\Delta AG/\Delta HCO_3^-$ ratio be used to diagnose mixed disturbance? Some authors, using the data from Adrogué et al.,[12] suggested that mixed disturbances should be considered if the ratio is <0.8 or >1.2. Paulson, applying this rule to a group of normal control subjects and patients with simple metabolic acidosis, noted that the formula erroneously categorized 56% of this group as mixed disturbances. Use of the 95% confidence interval of ± 8 mEq/L increased the specificity to 97% but with a poor sensitivity of only 27%.[13] In addition, one should be cautious in applying these rules developed in DKA to patients with other types of metabolic acidosis. Oh et al.[11] found a *mean* ratio close to unity in a group of patients with DKA but as high as 1.6 in patients with phenformin-induced lactic acidosis. This is probably due to the lower renal clearance of lactate compared with keto-anions. It is interesting that in exercise-induced lactic acidosis, the ratio remains close to unity up to a serum lactate of 15 mEq/L but increases significantly as the lactate level rises further and serum pH drops below 7.15.[14] This finding may be due to better buffering at lower pH by nonbicarbonate buffers, including hemoglobin. The difference between DKA and lactic acidosis,

however, is multifactorial and reflects the differences in distribution space, renal clearance, duration, and severity of acidosis as well as volume status.

Given the complexity in the relationship between ΔAG and ΔHCO_3^-, how, then, should clinicians use this ratio? I think we should abandon diagnosing mixed disturbance *solely* on the basis of the use of $\Delta AG/\Delta HCO_3^-$ ratio of <0.8 or >1.2. Although the confidence interval derived by Paulson provides greater specificity, it has poor sensitivity and should therefore be used cautiously.[15] To diagnose a mixed acid-base disorder, we therefore need to use all available data and not depend on a single formula. I therefore suggest the following:

1. Know the normal AG range for your laboratory.

2. Correct the AG for serum albumin concentration, and always use corrected AG.

3. Compare the AG with the baseline AG in your patient rather than with a normal range.

4. Use all clinical information, including historical and laboratory data, in making a diagnosis of mixed acid-base disturbance.

5. Follow patients with a complex presentation carefully because the diagnosis of a hidden disorder(s)

may become apparent by evaluating response to therapy.

6. Use the $\Delta AG/\Delta HCO_3^-$ ratio or $\Delta\Delta$ as one piece of evidence among many in making your final diagnosis. Be aware of its limitations as discussed here.

DISCLOSURES

None.

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