Some Observations on the Clinical Approach to Metabolic Acidosis

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The first step in the clinical approach to patients with metabolic acidosis is to deal with emergencies and to anticipate and prevent dangers associated with therapy. The traditional clinical analysis for the presence of metabolic acidosis suffers from a number of limitations that at times hinders one’s ability to reach a proper diagnosis. Our aim here is to raise awareness of some of the nuanced difficulties and illustrate why other considerations add value.

In patients with metabolic acidosis, analyses based on the anion gap in plasma (Panion gap) or the strong ion difference have major deficiencies. For example, the diagnosis of metabolic acidosis may be missed if one relies solely on pH and the concentration of bicarbonate (HCO₃⁻) in plasma (pHCO₃) without considering changes in the content of HCO₃⁻ in the extracellular fluid (ECF) compartment. In addition, the rules of respiratory compensation, which are based solely on the arterial PCO₂ rather than the more valuable PCO₂ in capillary blood-draining skeletal muscle (as reflected by the venous PCO₂), fail to assess the effectiveness of the bulk of the bicarbonate buffer system to remove H⁺ and, hence, whether more H⁺ will bind to intracellular proteins in vital organs, such as the brain or the heart.

DIAGNOSIS OF METABOLIC ACIDOSIS

The traditional definition of metabolic acidosis is based on a low pH in plasma, a low pHCO₃, and a high value for the Panion gap if its basis is added acids. A major decrease in ECF volume (ECFV), however, will raise the pHCO₃ because this parameter is the ratio of the content of HCO₃⁻ in the ECF compartment to the ECFV. This explains why the diagnosis of metabolic acidosis was missed in a patient with diabetic ketoacidosis and a very low ECFV, for whom the provisional diagnosis was hyperglycemic hyperosmolar nonketotic coma. In fact, this error was revealed by calculation of the content of HCO₃⁻ in the ECF compartment. Failure to recognize the presence of metabolic acidosis led to a severe degree of acidemia when the ECFV was re-expanded with a solution that did not contain HCO₃⁻ or one of its precursors, organic anions that undergo metabolism to neutral end products. Moreover, pulmonary edema developed in this patient before his intravascular volume was re-expanded completely. Perhaps the development of acidemia led to constriction of the venous capacitance vessels and hence a significant increase in central blood volume.

We suggest that one must calculate the content of HCO₃⁻ in the ECF compartment to deduce whether metabolic acidosis is present when there is a significantly contracted ECFV. A quantitative assessment of the ECFV is required for this purpose. Because the physical examination cannot reveal the degree of contraction of the ECFV in quantitative terms, the best available technique for this purpose at the bedside is one that depends on a rise in the concentration of red blood cells (RBCs) by examining the hematocrit or hemoglobin concentration or a rise in total plasma proteins. For example, a hematocrit of 0.50 suggests that there is a 33% decline in the plasma volume (a change from 2 L of RBCs plus 3 L of plasma to 2 L of RBCs plus 2 L of plasma), whereas a hematocrit of 0.60 suggests that the plasma volume declined by >50%, to 1.33 L.

DETECTION OF ADDED ACIDS BY FINDING NEW ANIONS

There are two issues in this context. The first is finding that new anions are present in a patient with metabolic acidosis using the Panion gap or strong ion difference to suggest that metabolic acidosis was in the near-normal range. Again, this error was revealed by calculation of the content of HCO₃⁻ in the ECF compartment. Failure to recognize the presence of metabolic acidosis led to a severe degree of acidemia when the ECFV was re-expanded with a solution that did not contain HCO₃⁻ or one of its precursors, organic anions that undergo metabolism to neutral end products. Moreover, pulmonary edema developed in this patient before his intravascular volume was re-expanded completely. Perhaps the development of acidemia led to constriction of the venous capacitance vessels and hence a significant increase in central blood volume.
acidity is due to added acids. Although it is common to adjust
the baseline value of the \( P_{\text{anion gap}} \) for the concentration of albu-
mmin in plasma (\( P_{\text{albumin}} \)) in patients with a low \( P_{\text{albumin}} \), similar
adjustments must be made in patients with high \( P_{\text{albumin}} \). In ad-
dition, when the effective arterial blood volume (EABV) is con-
tracted, there is a larger net anionic charge on the \( P_{\text{albumin}} \). When
detecting new anions, one assumes that the anionic contribution
of plasma proteins can be deduced from the \( P_{\text{albumin}} \), but this is
not always true when other plasma proteins bear a positive net
charge, such as in a patient with multiple myeloma. Conversely,
if new acids are added and their anions are largely excreted,
their concentrations are often low in plasma and high in the
urine—examples include hippurate anions in patients sniffing
glue or ketoacid anions in patients with diabetic ketoacidosis
and well-preserved GFRs. Hence, the hunt for new anions
should examine their loss through the urine.

In this process, the concentration of new anions is equal to
the sum of the usual urine cations that are present in abundant
amounts (\( \text{Na}^+ + \text{K}^+ + \text{NH}_4^+ \)) minus the major anion in the
urine, chloride (\( \text{Cl}^- \)). Although there are other anions in the
urine that are not included in this formula (in particular,
\( \text{H}_2\text{PO}_4^- \) and \( \text{SO}_4^{2-} \)), the purpose of this formula is to detect
conditions with acid overproduction in which there is a very
high rate of excretion of the accompanying anion in the urine.
Hence, the usual rates of excretion of other anions would be
relatively low and should not negate the usefulness of this for-
mula to detect new anions in the urine. The concentration of
\( \text{NH}_4^+ \) can be estimated with the urine osmolal gap (see equa-
tions in the next paragraph).14

In our view, the urine osmolal gap is the best indirect test to
detect a high rate of excretion of \( \text{NH}_4^+ \) in the urine. We em-
phasize that when using this calculation, the question asked is,
“Is there a high rate of excretion of \( \text{NH}_4^+ \) in the urine?” In
normal individuals who are given an acid load for several days,
the rate of excretion of \( \text{NH}_4^+ \) rises to approximately 200
mmol/d. In the presence of a high rate of excretion of \( \text{NH}_4^+ 
\), plus accompanying anion, the contribution of other urine os-
moles will be relatively small and should not affect the validity
of this test for clinical purposes. Parenthetically, the study by
Meregalli et al.,15 which questioned the accuracy of the urine
osmolal gap to estimate the concentration of \( \text{NH}_4^+ \) in the
urine, was carried out in normal individuals in whom the con-
centration of \( \text{NH}_4^+ \) was \(<10 \text{ mmol/L} \) to approx-
imately 50 mmol/L. Thus, it did not address the usefulness of
this calculation in the estimation of the concentration of \( \text{NH}_4^+ 
\) in the urine when the rate of excretion of \( \text{NH}_4^+ \) was appropri-
ately high. Hence, that study does not negate the usefulness of
our use of the urine osmolal gap to estimate \( U_{\text{NH}_4}/U_{\text{NH}_4} = 0.5 \)
(measured \( U_{\text{Osm}} - \text{calculated } U_{\text{Osm}} \)), where the calculated
\( U_{\text{Osm}} = 2 (U_{\text{Na}} + U_{\text{K}}) + U_{\text{urea}} \). Calculation of \( U_{\text{Osm}} \)
should include the concentration of glucose in the urine in a patient
with hyperglycemia.

In summary, we suggest that the baseline value of \( P_{\text{anion gap}} \)
should also be adjusted in patients with a high \( P_{\text{albumin}} \). The net
anionic charge on \( P_{\text{albumin}} \) or total plasma proteins becomes
more negative when the EABV is low,14 but there is no quan-
titative adjustment for this at the bedside. New anions may be
detected in the urine by calculating the urine anion gap (\( \text{Na}^+
+ \text{K}^+ + \text{NH}_4^+ - \text{Cl}^- \) in mEq/L).16

The second issue is the 1:1 ratio between the rise in \( P_{\text{anion gap}} \)
and the fall in \( P_{\text{HCO}_3^-} \) in patients with metabolic acidosis as a
result of added acids. Although it is useful to compare the change
in the \( P_{\text{anion gap}} \) with that of the \( P_{\text{HCO}_3^-} \) to detect mixed
metabolic acid-base disorders, this will also lead to underesti-
mation of the magnitude of the \( \text{HCO}_3^- \) deficit—the added \( \text{H}^+ 
\) load—if the ECFV is contracted, because these calculations are
based on concentration terms and hence do not reflect the change
in content of \( \text{HCO}_3^- \) (Table 1).

Table 1. Changes in the content of \( \text{HCO}_3^- \) and new anions in the ECF
compartment

<table>
<thead>
<tr>
<th>Condition</th>
<th>ECF Volume (L)</th>
<th>( \text{HCO}_3^- ) Concentration (mmol)</th>
<th>( \text{HCO}_3^- ) Content (mmol)</th>
<th>( K^+ ) Concentration (mmol)</th>
<th>( K^+ ) Content (mmol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>10</td>
<td>25</td>
<td>250</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DKA</td>
<td>8</td>
<td>10</td>
<td>80</td>
<td>15</td>
<td>120</td>
</tr>
<tr>
<td>Balance</td>
<td>-2</td>
<td>-170</td>
<td>+170</td>
<td>-15</td>
<td>+120</td>
</tr>
</tbody>
</table>

To illustrate this point, we use a patient with diabetic ketoacidosis (DKA) as an example. In these
calculations, we ignored changes in the \( P_{\text{albumin}} \) for simplicity. Note that although there is a 1:1 ratio
between the fall in \( P_{\text{HCO}_3^-} \) and the rise in the concentration of ketoacid anions in plasma (\( K^+ \)),
which is reflected by the rise in \( P_{\text{anion gap}} \), the deficit of \( \text{HCO}_3^- \) is significantly larger than can be estimated
from the gain of \( K^+ \) in the urine by calculating the urine anion gap (\( \text{Na}^+ + \text{K}^+ + \text{NH}_4^+ - \text{Cl}^- \) in mEq/L).16

Acidemia stimulates the respiratory center, which increases
tidal volume to produce a quantitative decrease in the arterial
\( P_{\text{CO}_2} \). The fall in this \( P_{\text{CO}_2} \) is required for optimal removal of
\( H^+ \) by the bicarbonate buffer system, and there are a number of proposed formulas
relating changes in the arterial \( P_{\text{CO}_2} \) to the blood \( \text{pH} \) or \( P_{\text{HCO}_3^-} \). Nevertheless, we do not
emphasize these equations in this article, because they do not reflect the cap-
illary \( P_{\text{CO}_2} \) and the adequacy of \( H^+ \) removal by the bulk of the bicarbonate buffer
system.3

It is the \( P_{\text{CO}_2} \) in skeletal muscle capillar-
ies that must be low to permit the removal of the vast majority of \( H^+ \) by the bicarbonate
buffer system. When this latter \( P_{\text{CO}_2} \) is too high, acidemia will be more pronounced and
more of the \( H^+ \) load must be titrated in
the brain and the heart (Figure 1). Binding of \( H^+ \) to intracellular proteins will change
their charge, shape, and perhaps their functions; therefore, the major clinical settings for failure of the bicarbonate buffer system in skeletal muscles, providing that their capillary PCO₂ is low. Notwithstanding, in a patient who has metabolic acidosis and has a contracted EABV, as in this example, the PCO₂ in the muscle capillary blood will be high (50 mmHg, which is 20 mmHg greater than the arterial PCO₂ of 30 mmHg). Hence, fewer H⁺ can be removed by the bicarbonate buffer system in skeletal muscle. As a result, the circulating H⁺ concentration rises (large bold H⁺ symbol), which increases the H⁺ burden for brain cells and thereby the binding of H⁺ to proteins (PTNH⁺) in brain cells (and also in muscle cells).³ This binding of an appreciable portion of this H⁺ load to proteins in the brain will be reversed when PCO₂ in muscle capillary blood declines (i.e., when the EABV is re-expanded).

Figure 1. Consequences of failure of bicarbonate buffer system in a patient with metabolic acidosis and a low effective arterial blood volume. The cylindrical structure on the left is a capillary draining skeletal muscle (central oval structure), whereas the circle to its right represents the brain. After an acid load, the vast majority of the H⁺ load will be removed by the bicarbonate buffer system in skeletal muscles, providing that their capillary PCO₂ is low. Notwithstanding, in a patient who has metabolic acidosis and has a contracted EABV, as in this example, the PCO₂ in the muscle capillary blood will be high (50 mmHg, which is 20 mmHg greater than the arterial PCO₂ of 30 mmHg). Hence, fewer H⁺ can be removed by the bicarbonate buffer system in skeletal muscle. As a result, the circulating H⁺ concentration rises (large bold H⁺ symbol), which increases the H⁺ burden for brain cells and thereby the binding of H⁺ to proteins (PTNH⁺) in brain cells (and also in muscle cells).³ This binding of an appreciable portion of this H⁺ load to proteins in the brain will be reversed when PCO₂ in muscle capillary blood declines (i.e., when the EABV is re-expanded).

Table 2. Recommended changes in the clinical approach to metabolic acidosis

<table>
<thead>
<tr>
<th>Issues</th>
<th>Traditional Views</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition of metabolic acidosis</td>
<td>A process that tends to lower the P₇HCO₃</td>
<td>One must estimate the content of HCO₃⁻ in the ECF compartment when the patient has contracted ECFV. Adjust P₇anion gap, when Palbumin is high. Valence on Palbumin is higher if the EABV is low. Detect new anions in urine, use urine anion gap (Na⁺ + K⁺ + NH₄⁺ - Cl⁻) UOsm gap is the best indirect test to detect UNH₄. Calculate HCO₃⁻ content in ECFV to estimate its deficit if the ECFV is low. Use the capillary PCO₂ in skeletal muscles (reflected by brachial venous PCO₂).</td>
</tr>
<tr>
<td>Look for the presence of new anions</td>
<td>Uses the P₇anion gap or SID</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adjusts baseline value of P₇anion gap, when Palbumin is low</td>
<td></td>
</tr>
<tr>
<td>Detect NH₄⁺ in the urine</td>
<td>Use urine pH and urine anion gap (Na⁺ + K⁺ + NH₄⁺ - Cl⁻)</td>
<td></td>
</tr>
<tr>
<td>Compare fall in P₇HCO₃ with rise in P₇anion gap</td>
<td>Expect a 1:1 ratio in the fall in the P₇HCO₃ and the rise in the P₇anion gap</td>
<td></td>
</tr>
<tr>
<td>Examine effectiveness of the bicarbonate buffer system</td>
<td>Relies exclusively on the arterial PCO₂</td>
<td></td>
</tr>
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The critique applies equally to the P₇anion gap and strong ion difference (SID) approaches.
min. At times, new anions may be excreted promptly in the urine when they can be secreted or filtered and poorly reabsorbed. A high rate of excretion of new anions in the urine is detected using the calculation of the urine anion gap; the concentration of $\text{NH}_4^+$ can be estimated with the urine osmolal gap, as described already. The brachial or femoral venous $\text{PCO}_2$ rather than the arterial $\text{PCO}_2$ must be used to assess the effectiveness of the bicarbonate buffer system to remove $\text{H}^+$. 

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DISCLOSURES

None.

REFERENCES