Bicarbonate Therapy in Severe Metabolic Acidosis

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ABSTRACT
The utility of bicarbonate administration to patients with severe metabolic acidosis remains controversial. Chronic bicarbonate replacement is obviously indicated for patients who continue to lose bicarbonate in the ambulatory setting, particularly patients with renal tubular acidosis syndromes or diarrhea. In patients with acute lactic acidosis and ketoacidosis, lactate and ketone bodies can be converted back to bicarbonate if the clinical situation improves. For these patients, therapy must be individualized. In general, bicarbonate should be given at an arterial blood pH of ≤7.0. The amount given should be what is calculated to bring the pH up to 7.2. The urge to give bicarbonate to a patient with severe acidemia is apt to be all but irresistible. Intervention should be restrained, however, unless the clinical situation clearly suggests benefit. Here we discuss the pros and cons of bicarbonate therapy for patients with severe metabolic acidosis.


Metabolic acidosis is an acid-base disorder characterized by a primary consumption of body buffers including a fall in blood bicarbonate concentration. There are many causes (Table 1), and there are multiple mechanisms that minimize the fall in arterial pH. A patient with metabolic acidosis may have a normal or even high pH if there is another primary, contravening event that raises the bicarbonate concentration (vomiting) or lowers the arterial PCO₂ (respiratory alkalosis). Metabolic acidosis differs from “acidemia” in that the latter refers solely to a fall in blood pH and not the process.

A recent online survey by Kraut and Kurtz¹ highlighted the uncertainty over when to give bicarbonate to patients with metabolic acidosis. They reported that nephrologists will prescribe therapy at a higher pH compared with critical care physicians. Forty percent of the intensivists would not give bicarbonate unless the pH were <7.0; only 6% of nephrologists would wait until pH gets this low (P < 0.01). Also, >80% of nephrologists would consider the PCO₂ in making their decision to treat, whereas only 59% of intensivists would (P < 0.02). For patients with lactic acidosis, 86% of nephrologists would treat with bicarbonate, whereas two thirds of intensivists would give bicarbonate (P < 0.05). A wider variance was noted in the therapy of diabetic ketoacidosis. Sixty percent of nephrologists would treat with bicarbonate versus 28% of intensivists (P < 0.01). Both groups would administer bicarbonate by constant infusion, targeting an arterial pH of 7.2 as a goal. Seventy-five percent of nephrologists would calculate the amount of bicarbonate required, whereas only one third of intensivists would do this.

Metabolic acidosis results from a loss of bicarbonate from the body (e.g., diarrhea) or from its titration to an anionic base that often can be converted back to bicarbonate, such as seen in diabetic ketoacidosis or lactic acidosis (Table 1). This nonbicarbonate base anion is commonly termed “potential” bicarbonate. Giving bicarbonate to a patient with a true bicarbonate deficit is not controversial. Controversy arises when the decrease in bicarbonate concentration is the result of its conversion to another base, which, given time, can be converted back to bicarbonate. If one knew that the timely and efficient conversion of acetacetate and β-hydroxybutyrate or lactate back to bicarbonate would occur without morbidity or mortality, then there would be no reason even to contemplate giving bicarbonate.

In considering acute bicarbonate replacement, four questions should be considered: (1) What are the deleterious effects of acidemia, and when are they manifest? (2) When is acidemia severe enough to warrant therapy? (3) How much bicarbonate should be given, and how is that amount calculated? (4) What are the deleterious effects of bicarbonate therapy?

Severe acidemia causes a decrease in myocardial contractility, a fall in cardiac output, and a fall in BP. Acidemia also decreases the binding of norepinephrine to its receptors. It also shifts the oxyhemoglobin curve to the right, allowing more O₂ to be released—the Bohr Effect. Protons bind to intracellular proteins as well as extracellular proteins, especially...
The optimum extracellular pH for all physiologic mechanisms and organ functions is 7.4. By contrast, intracellular pH is approximately 7.1 in virtually every tissue studied. Many diverse mechanisms are in place to maintain both extracellular and intracellular pH within this very narrow range. Deviations from normal pH will obviously decrease the efficiency of all reactions, although the degree will vary depending on the specific event. For example, whereas acidemia protects the central nervous system against seizures, it sensitizes the myocardium to arrhythmias. Because we do not measure intracellular pH, we must use extracellular pH (arterial or venous) as a surrogate. Most authorities in acid-base physiology would give bicarbonate to a patient with an arterial pH <7.1, but, as we discuss, this is not a hard and fast rule.

The volume of distribution of bicarbonate is approximately that of total body water. In patients with metabolic acidosis, it is said to vary from 50% to >100%, depending on the severity of the acidemia.6 This distribution will obviously affect the calculated bicarbonate deficit. Any calculated amount will be only approximate, of course. The patient should be carefully monitored and bicarbonate administration altered, when given, to suit the course. Fernandez et al.7 derived a more precise formula for calculating the bicarbonate space: (0.4 + 2.6/PCO2 (body weight). A graphic representation of the formula (Figure 5 in reference7) shows that the “apparent” bicarbonate space increases quite markedly with acidemia but decreases very little with alkalemia. Although they used actual data from several human studies, it is not clear that renal response to acidemia was accounted for as they analyzed acute acid-base disorders. This formula, like any other guide to bicarbonate treatment, should just be a starting point, which is modified as events unfold.

In some patients, only a small amount of bicarbonate may be required. For example, if a patient has a PCO2 of 13 mmHg and bicarbonate of 4 mEq/L, then his arterial pH is 7.1. If the bicarbonate is doubled (raised to only 8 mEq/L), then the blood pH will increase to 7.4. This is true only if the PCO2 does not change. In this example, a static PCO2, if the bicarbonate concentration rises only 1 mEq/L, then the pH would be above 7.2. Arterial PCO2 typically, however, does not remain the same after NaHCO3 infusion. In patients with severe acidosis, it rises 6.7 ± 1.8 mmHg when an infusion of sodium bicarbonate is given (1.5 mmol/kg over 5 min).8 By contrast, infusion with THAM® (Hospital Inc., Lake Forest, IL) or CarbiCarb® (International Medication System, South El Monte, CA) does not affect arterial Pco2.6,9 These observations have led some investigators to recommend either of these compounds as preferred therapy.2

Bicarbonate therapy is also associated with an increase in mortality. This has been noted in humans and experimental animals under a variety of acidic conditions.10–12 The increase in mortality is blamed on a fall in BP and cardiac output. There are also shifts in ionized calcium; in strong acid acidosis, potassium also shifts out of the cell sensitizing the heart to abnormal electrical activity and subsequent arrhythmias. Moreover, a “paradoxical” intracellular acidosis may occur when giving bicarbonate therapy because CO2 generated from its titration freely diffuses across the cell membrane. In addition, both volume expansion and hypernatremia can occur; in patients with compromised cardiac output, fulminate congestive heart failure with flash pulmonary edema may result.

Many in vitro studies show that intracellular alkalization hastens cell death after anoxia17; if cell water is maintained at pH 6.8, for example, more tissue remains viable.14,15 Bicarbonate administration may stimulate superoxide formation, increase proinflammatory cytokine release, or enhance apoptosis. Whether these observations relate to human disorders with acidemia is unknown. Rebound alkalemia may also occur after base administration, especially when the PCO2 is low. Giving bicarbonate to both animals and humans increases blood lactate and ketone bodies.6,16–18 This “potential” bicarbonate will be converted back to actual bicarbonate unless it lost in the urine.

### DIABETIC KETOACIDOSIS

In ketoacidosis, substantial amounts of acetoacetate and β-hydroxybutyrate are lost in the urine before the patient arrives at the hospital. Thus, not only has the

### Table 1. Causes of severe metabolic acidosis

<table>
<thead>
<tr>
<th>General Mechanism</th>
<th>Specific Clinical Examples</th>
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<tbody>
<tr>
<td>True HCO3 deficit</td>
<td>Renal tubular acidosis</td>
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<tr>
<td>kidney</td>
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<tr>
<td>gastrointestinal</td>
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<td>H+ gain</td>
<td>NH4Cl administration, toxins</td>
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<td>exogenous acid</td>
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<td>abnormal lipid metabolism</td>
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<td>abnormal carbohydrate metabolism</td>
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<td>normal protein metabolism</td>
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*Also a component of true HCO3 deficit because ketone bodies (“potential” HCO3) are lost in the urine both before and after admission.
patient converted bicarbonate to “poten-
tial bicarbonate,” he is truly bicarbonate
deficient. More urinary loss of ketone
bodies occurs after fluid administration
and volume repletion. Hence, the ubiqui-
tuous hyperchloremic metabolic acido-
sis we see the day after insulin therapy is
initiated. In ketoacidosis, it is almost
never necessary to give bicarbonate even
though the patient is bicarbonate defi-
cient unless renal function is perma-
nently impaired. Therapy with fluids and
electrolytes restores extracellular volume
and renal blood flow, thus enhancing the
renal excretion of acid and regenerating bicarbonate. Okuda et al. demonstrated
in humans with diabetic ketoacidosis, as well as in the in situ aci-
demic perfused rat liver (pH of 7.15), that bi-
carbonate therapy markedly increased
blood acetoacetate and β-hydroxybuty-
trye levels. Infusion also increased blood lactate levels approximately three-
fold. Others have reported similar find-
ings. Indeed, bicarbonate therapy actu-
ally delays the removal of ketone bodies
from the blood.

LAETIC ACIDOSIS

Lactic acidosis is an ominous event and
generally signifies severe tissue hypoxia.
It may be secondary to an exogenous
toxin such as cyanide or metformin or
the result of severe tissue underperfusion
from cardiogenic or hemorrhagic shock.
The mortality of lactic acidosis ap-
proaches 80% or more. This is often be-
cause of the inability to correct ade-
quately the underlying disorder(s). A
number of studies show even if blood
lactate level is lowered with drug therapy,
mortality is unchanged.

CASE EXAMPLES

The following two cases demonstrate
that therapy for acidemia requires flexi-
bility.

Patient 1
A 20-yr-old man with a 5-yr history of
type 1 diabetes was admitted for the
ninth time in diabetic ketoacidosis. He
was poorly responsive and had Kussmaul
respirations. Before any therapy, he had a
plasma Na of 140 mEq/L, K of 4 mEq/L,
Cl of 109 mEq/L, CO₂ of 3 mEq/L, and
creatinine of 1 mg/dl. The arterial pH
was 6.95, Pco₂ was 14 mmHg, and the
calculated HCO₃ was 3 mEq/L. Urine
and blood ketones were strongly posi-
tive. He was treated with insulin and ap-
propriate fluid and electrolyte replace-
ment. He was not given bicarbonate. The
next day he was fully oriented. His
plasma Na was 142, K was 4, Cl was 114,
and CO₂ was 18 mEq/L. The remainder of
his clinical course was unremarkable.

Patient 2
An 80-yr-old man was admitted with se-
vere congestive heart failure. He was hy-
potensive and oliguric. He had both pul-
monary and peripheral edema. His
baseline creatinine was known to be 1.6
mg/dl. On arrival at the emergency de-
partment, his plasma Na was 135 mEq/L,
K was 4 mEq/L, Cl was 97 mEq/L, CO₂
was 7 mEq/L, and creatinine was 2.5 mg/
dl. His arterial pH was 7.1, Pco₂ was 20
mmHg, and the calculated HCO₃ was 6
mEq/L. The blood lactate level was 20
mmol/L. The patient was intubated and
placed on a respirator, keeping his Pco₂
at 20 mmHg. Continuous venovenous
hemodialysis was begun with a bath con-
taining 14 mEq/L of bicarbonate. He
was given an infusion of 300 mEq of bi-
carbonate over 2 h; with a total body water
of 43 L, one would aim for an HCO₃ of 14
mEq/L: (7 mEq/L × 43 L = 301 mEq). At
the end of that time, his pH was 7.2 and
the HCO₃ was 13 mEq/L. Five days later,
he was transferred out of the intensive
care unit, his lactic acidosis resolved.

FINAL THOUGHTS

Bicarbonate therapy for metabolic aci-
dosis is recommended at an arterial pH
varying from as low as 6.9 to as high as
7.2. We suggest that bicarbonate therapy
be given at pH 7.0 but that this target pH
be a guide that is variable depending on
clinical setting. Unless efforts are focused
on reversing the underlying defects re-
sponsible for the acidosis, base therapy
will be futile.

If bicarbonate is given, then its
amount should be calculated as the de-
sired minus the observed bicarbonate
concentration using a volume of distri-
bution of total body water. It should also
be assumed that the arterial Pco₂ will not
change. The desired bicarbonate concen-
tration at this unchanged Pco₂ is that
which will give an arterial pH of 7.2. This
calculation is only an approximation. At
the end of 2 h, an arterial blood gas and
chemistries should be remeasured and a
new plan for the next 2 h made. Note that
patient 1 got no bicarbonate. He was oth-
erwise healthy with a normal cardiovas-
cular system, whereas patient 2 received
bicarbonate because he had a severely
compromised cardiovascular system.
Thus, it is impossible to be dogmatic
about the treatment of acidemia. No
hard and fast rule works for every pa-
tient.

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Bicarbonate and Metabolic Acidosis