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 PCO$_2$ (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 Kurtz$^1$ 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 PCO$_2$ 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 O$_2$ to be released—the Bohr Effect. Protons bind to intracellular proteins as well as extracellular proteins, especially
Table 1. Causes of severe metabolic acidosis

<table>
<thead>
<tr>
<th>General Mechanism</th>
<th>Specific Clinical Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>True HCO₃ deficit</td>
<td>Renal tubular acidosis</td>
</tr>
<tr>
<td>kidney</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>gastrointestinal</td>
<td></td>
</tr>
<tr>
<td>H⁺ gain</td>
<td>NH₄Cl administration, toxins</td>
</tr>
<tr>
<td>exogenous acid</td>
<td>Diabetic ketoacidosis*</td>
</tr>
<tr>
<td>abnormal lipid metabolism</td>
<td>Lactic acid</td>
</tr>
<tr>
<td>abnormal carbohydrate metabolism</td>
<td>Uremic acid</td>
</tr>
<tr>
<td>normal protein metabolism</td>
<td></td>
</tr>
</tbody>
</table>

*Also a component of true HCO₃ deficit because ketone bodies (“potential” HCO₃) are lost in the urine both before and after admission.

albumin and hemoglobin. Thus, acidemia may adversely affect cell functions such as enzymatic reactions, ATP generation, fatty acid biosynthesis, and bone formation/resorption.⁵⁻⁷

All drugs that are the salts of weak bases or acids have a dissociation constant. Those that are the salts of a weak acid will have more of the drug in the nonionized form in an acid environment and, thus, may manifest increased toxicity. One such example of enhanced toxicity during acidemia is that of acetylsalicylic acid. Other salts of weak acids are tolbutamide, methotrexate, phenobarbital, and phenytoin. The degree of ionization is only one of the factors that determine a drug’s solubility across cell membranes, but it is crucial in those body compartments in which pH may change.⁵

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, given 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 acidemic 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 anoxia;¹³ 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
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.\(^18\) demon-
strated in humans with diabetic ketoaci-
dosis, as well as in the in situ acidemic
perfused rat liver (pH of 7.15), that bi-
carbonate therapy markedly increased
blood acetoacetate and β-hydroxybut-
trate levels. Infusion also increased
blood lactate levels approximately three-
fold. Others have reported similar find-
ings.\(^19\) Indeed, bicarbonate therapy actu-
ally delays the removal of ketone bodies
from the blood.

**LACTIC 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.\(^17,20,21\)

**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, CO\(_2\) of 3 mEq/L, and
creatinine of 1 mg/dl. The arterial pH was 6.95, P\(_{CO2}\) was 14 mmHg, and the
calculated H\(_{CO3}\) was 3 mEq/L. Urine
acetoacetate and β-hydroxybutyrate
were strongly positive. 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 CO\(_2\) 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, CO\(_2\)
was 7 mEq/L, and creatinine was 2.5 mg/
dl. His arterial pH was 7.1, P\(_{CO2}\) was 20
mmHg, and the calculated H\(_{CO3}\) was 6
mEq/L. The blood lactate level was 20
mmol/L. The patient was intubated and
placed on a respirator, keeping his P\(_{CO2}\)
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 H\(_{CO3}\) of 14
mEq/L: (7 mEq/L × 43 L = 301 mEq). At
the end of that time, his pH was 7.2 and
the H\(_{CO3}\) 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 am-
ount 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 P\(_{CO2}\) will not
change. The desired bicarbonate concen-
tration at this unchanged P\(_{CO2}\) 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.

**DISCLOSURES**

None.

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