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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.

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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 P_{CO_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 P_{CO_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 acetoacetate 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

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Table 1. Causes of severe metabolic acidosis

General Mechanism	Specific Clinical Examples
True HCO_3 deficit	
kidney	Renal tubular acidosis
gastrointestinal	Diarrhea
H^+ gain	
exogenous acid	NH_4Cl administration, toxins
abnormal lipid metabolism	Diabetic ketoacidosis[a]
abnormal carbohydrate metabolism	Lactic acid
normal protein metabolism	Uremic acidosis

[a]Also a component of true HCO_3 deficit because ketone bodies ("potential" HCO_3) 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.[2–4]

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: $(0.4 + 2.6/P_{HCO_3})$ (body weight). A graphic representation of the formula (Figure 5 in reference[7]) 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 P_{CO_2} 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 P_{CO_2} does not change. In this example, given a static P_{CO_2}, if the bicarbonate concentration rises only 1 mEq/L, then the pH would be above 7.2. Arterial P_{CO_2} typically, however, does not remain the same after $NaHCO_3$ 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® (Hospira Inc., Lake Forest, IL) or CarbiCarb® (International Medication System, South El Monte, CA) does not affect arterial P_{CO_2}.[8,9] 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 "paradoxic" intracellular acidosis may occur when giving bicarbonate therapy because CO_2 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 alkalinization 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 P_{CO_2} 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 "potential bicarbonate," he is truly bicarbonate deficient. More urinary loss of ketone bodies occurs after fluid administration and volume repletion. Hence, the ubiquitous hyperchloremic metabolic acidosis 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 deficient unless renal function is permanently 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] demonstrated in humans with diabetic ketoacidosis, as well as in the *in situ* acidemic perfused rat liver (pH of 7.15), that bicarbonate therapy markedly increased blood acetoacetate and β-hydroxybutyrate levels. Infusion also increased blood lactate levels approximately threefold. Others have reported similar findings.[19] Indeed, bicarbonate therapy actually 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 approaches 80% or more. This is often because of the inability to correct adequately 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 flexibility.

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_{CO_2} was 14 mmHg, and the calculated HCO_3 was 3 mEq/L. Urine and blood ketones were strongly positive. He was treated with insulin and appropriate fluid and electrolyte replacement. 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 severe congestive heart failure. He was hypotensive and oliguric. He had both pulmonary and peripheral edema. His baseline creatinine was known to be 1.6 mg/dl. On arrival at the emergency department, 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_{CO_2} was 20 mmHg, and the calculated HCO_3 was 6 mEq/L. The blood lactate level was 20 mmol/L. The patient was intubated and placed on a respirator, keeping his P_{CO_2} at 20 mmHg. Continuous venovenous hemodialysis was begun with a bath containing 14 mEq/L of bicarbonate. He was given an infusion of 300 mEq of bicarbonate over 2 h; with a total body water of 43 L, one would aim for an HCO_3 of 14 mEq/L: ($7 \text{ mEq/L} \times 43 \text{ L} = 301 \text{ mEq}$). At the end of that time, his pH was 7.2 and the HCO_3 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 acidosis 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 responsible for the acidosis, base therapy will be futile.

If bicarbonate is given, then its amount should be calculated as the desired minus the observed bicarbonate concentration using a volume of distribution of total body water. It should also be assumed that the arterial P_{CO_2} will not change. The desired bicarbonate concentration at this unchanged P_{CO_2} 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 otherwise healthy with a normal cardiovascular 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 patient.

DISCLOSURES

None.

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