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Uses and misuses of sodium bicarbonate in the neonatal intensive care unit

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A B S T R A C T

Over the past several decades, bicarbonate therapy continues to be used routinely in the treatment of acute metabolic acidosis in critically ill neonates despite the lack of evidence for its effectiveness in the treatment of acid–base imbalance, and evidence indicating that it may be detrimental. Clinicians often feel compelled to use bicarbonate since acidosis implies a need for such therapy and thus the justification for its use is based on hearsay rather than science. This review summarizes the evidence and refutes the clinical practice of administering sodium bicarbonate to treat metabolic acidosis associated with several specific clinical syndromes in neonates.

1. Introduction

Sodium bicarbonate was first commercially available for use in the late 1950s, and soon thereafter its use in neonatal intensive care units (NICUs) became commonplace, not only for resuscitation of depressed newborn infants, but also as a therapy for correcting metabolic acidemia, and preventing azotemia, hypoglycemia, and elevations in serum potassium concentrations (the so-called Usher regimen) [1]. Despite limited data to recommend the practice, the use of sodium bicarbonate infusions during neonatal resuscitation and following cardiac arrest has continued. Moreover, sodium bicarbonate therapy may be detrimental. At the cellular level, increasing the bicarbonate concentration may not normalize intracellular pH but rather may paradoxically create a situation that lowers intracellular pH [2,3]. On the other hand, long-term administration of sodium bicarbonate has been efficacious in situations where metabolic acidosis is largely secondary to loss of bicarbonate from the kidney or gastrointestinal tract [4]. After a brief review of general acid–base physiology, several specific clinical syndromes in neonates are discussed in terms of acid–base physiology and physiological evidence with respect to bicarbonate therapy.

2. Extracellular and intracellular buffer systems and acid–base homeostasis in neonates

In general, acid–base homeostasis is tightly regulated by extracellular and intracellular buffer systems and respiratory and renal compensatory mechanisms of the organism. This involves various chemical and physiologic processes that maintain the acidity of body fluids at levels that allow optimal function of the whole individual. Chemical processes (buffering H^+ and hydrating CO_2) represent the first line of defense to an acid or alkali load and include the extracellular and intracellular buffers, whereas physiologic processes (pulmonary ventilation and renal acidification) modulate acid–base composition by changes in cellular metabolism and by adaptive responses in the excretion of volatile acids by the lungs and fixed acids by the kidneys. Clinicians track these intrinsic regulatory systems by measuring the difference between the normal range of buffer base in the body and the prevailing levels of buffer base in the patient's blood, referred to as 'base excess'. Base excess may be positive (indicating a relative excess of buffer base) or negative (indicating a reduction in the whole blood buffer base pool); the units are expressed as milliequivalents per liter (mEq/L). Blood buffering is accomplished by both bicarbonate and non-bicarbonate (hemoglobin, oxyhemoglobin, phosphates, and proteins) buffers. Total buffering capacity is divided approximately equally between the two buffer systems [5].

Bicarbonate acts as a buffer for H^+ by formation of carbonic acid (H_2CO_3) and its subsequent dissociation to H_2O and CO_2:

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$$HCO_3^- + H^+ \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2 \quad (1)$$

Bicarbonate levels are computed using the Henderson–Hasselbalch equation, which relates pH to the proportion of bicarbonate and H_2CO_3 acid:

$$pH = pKa + \log_{10}\left(\left[HCO_3^-\right] / [H_2CO_3]\right) \quad (2)$$

As the concentration of H_2CO_3 is related to the partial pressure of CO_2, and with the acid dissociation constant of carbonic acid being 6.1, the equation can be rewritten to relate pH to the ratio of HCO_3 and pCO_2:

$$pH = 6.1 + \log_{10}\left(\left[HCO_3^-\right] / 0.03 \times pCO_2\right) \quad (3)$$

From Equation (3) it can be seen that in order for blood pH to be maintained close to 7.4, the ratio of HCO_3^- to pCO_2 needs to be close to 20:1 ($\log_{10}$ of 20 being 1.3). Serum bicarbonate levels can be calculated with reasonable accuracy using this formula despite the variation in the dissociation constant of H_2CO_3 caused by the non-aqueous physical and chemical properties of whole blood and the methodologic limitations of the primary measurements. However, changes in total blood buffer base cannot be estimated accurately from bicarbonate levels alone without adjusting for non-bicarbonate buffering. Additionally, without correction for the hemoglobin concentration or, preferably, multipoint CO_2 titration data, the base deficit measurement and the bicarbonate measurement contain the same information. Most estimates of acid–base balance in the NICU do not take these covariates into account. Finally, it must be remembered that, although all buffers will equilibrate according to the isohydric principle, the time to equilibrium within the body is variable, and transient differences will necessarily exist among body compartments.

The intravascular fluid compartment communicates freely with the interstitium, which is roughly three times the size of the intravascular fluid and is buffered primarily by bicarbonate. The intracellular fluid compartment houses the metabolic machinery (mitochondria) and ultimately it is the mitochondrial pH that therapeutic manipulations of the blood buffer base are used to protect [6,7]. The intracellular fluid is buffered by a mixture of phosphates, protein, and bicarbonate. Experimental evidence suggests that 15–20% of an infusion of strong acid is buffered by the blood, 30% by the interstitium, and 55% by intracellular buffers [8], which implies that clinicians must monitor the quantitatively least important body buffer system and infer indirectly what is happening intracellularly.

Faced with a neonate with reduced stores of blood buffer base in the vascular space, the clinician should not attempt immediate replenishment. Once the limitations of the actual measurement are considered, ensuring that the numbers in the acid–base profile are consistent with the clinical condition of the neonate, one should focus on ways to address immediately the primary cause of the acid–base disturbance such as improving alveolar ventilation or oxygen transport. The clinician then should articulate specific therapeutic objectives with goals to reduce the acidosis in the microenvironment surrounding essential energy-generating organelles and assist the cell in restoring normal bioenergetics. In some clinical syndromes associated with metabolic acidosis in the neonate, a bicarbonate infusion will not meet the desired objectives of benefitting the neonate but may be associated with adverse outcomes of intraventricular hemorrhage [9], fluctuations in cerebral blood flow [10], worsening intracellular acidosis [2], aggravated myocardial injury [11], and deterioration of cardiac function [12], making the bicarbonate therapy not only useless but detrimental.

3. Role of bicarbonate therapy during cardiac arrest

Severe bradycardia or cardiac arrest leads to decreased cardiac output, poor perfusion, inadequate oxygen delivery to the tissues, depletion of intracellular energy stores, and ultimately metabolic acidosis. Early studies demonstrated decreased myocardial function and decreased myocardial sensitivity to catecholamines during acidosis [13]. The initial rise in H^+ ions in the face of decreased tissue oxygenation is mainly a consequence of hydrolysis of ATP during anaerobic glycolysis, with accumulation of lactic acid representing a late event. The liberated H^+ ions are buffered by both the bicarbonate and non-bicarbonate systems, and many have been tempted to replenish diminishing bicarbonate levels with administration of exogenous sodium bicarbonate. The argument for doing so is to maintain buffering ability against ongoing acid production, to correct presumed intracellular acidosis to optimize enzymatic function, and to correct acidemia in which endogenous and exogenous catecholamines are ineffective. Based on such rationales, sodium bicarbonate was frequently employed in cardiopulmonary resuscitation (CPR) long before any experimental evidence validated (or invalidated) these hypotheses.

Experimental models have established that administration of sodium bicarbonate may, under certain circumstances, result in a "paradoxical" intracellular acidification [3]. Addition of bicarbonate to the intravascular (i.e. extracellular) space will buffer excess H^+ ions by forming carbonic acid, which is further dissociated to water and CO_2. In situations where CO_2 cannot be rapidly eliminated from the local environment (i.e. in venous stasis or low perfusion states, as occur during cardiac arrest and CPR, when cardiac output is thought to be only 30% of normal), CO_2 accumulates, leading to local hypercarbia. Diffusion of CO_2 across the cell membrane occurs far more quickly than transport of HCO_3^-, resulting in initial overproduction of intracellular H^+ from carbonic acid. This intracellular acidification is the result of conversion of extracellular HCO_3^- to CO_2 by carbonic anhydrase. CO_2 ultimately diffuses across the cell membrane, resulting in intracellular acidosis. This reaction may be prevented by the addition of acetazolamide, a reversible inhibitor of carbonic anhydrase [3] (Fig. 1).

Levraut and colleagues further expanded on these observations and showed that the degree of intracellular acidification depended on the proportion of extracellular non-bicarbonate buffering capacity present, due to back-titration of the non-bicarbonate buffer [14,15]. Extracellular alkalization will therefore come at the price of intracellular acidification, which is often precisely the exact opposite of what the clinician had intended, and has two deleterious consequences. First, deepening of intracellular acidosis worsens myocardial contractility as H^+ ions compete with Ca^{2+} ions for binding to troponin. Second, extracellular alkalosis shifts the oxygen–hemoglobin saturation curve to the left, which impedes oxygen release to the tissues, exacerbating the situation.

These observations have been extended by animal models [16].

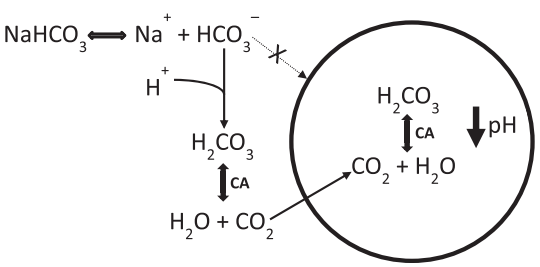

Fig. 1. The effect of abrupt rise in extracellular sodium bicarbonate concentration on intracellular pH. CA, carbonic anhydrase.

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