

Is there a role for sodium bicarbonate in treating lactic acidosis from shock?

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Purpose of review

Bicarbonate therapy for severe lactic acidosis remains a controversial therapy.

Recent findings

The most recent 2008 Surviving Sepsis guidelines strongly recommend against the use of bicarbonate in patients with pH at least 7.15, while deferring judgment in more severe acidemia. We review the mechanisms causing lactic acidosis in the critically ill and the scientific rationale behind treatment with bicarbonate.

Summary

There is little rationale or evidence for the use of bicarbonate therapy for lactic acidosis due to shock. We agree with the Surviving Sepsis guidelines recommendation against the use of bicarbonate for lactic acidosis for pH at least 7.15 and we further recommend a lower target pH of 7.00 or less. If bicarbonate is used, consideration must be given to slow infusion and a plan for clearing the CO₂ that is produced and measuring and correcting ionized calcium as the resultant 10% drop may decrease cardiac and vascular contractility and responsiveness to catecholamines. When continuous renal replacement therapy is used during severe acidosis, we recommend bicarbonate-based replacement fluid over citrate as citrate may increase the strong ion gap. Effective therapy of lactic acidosis due to shock is to reverse the cause.

Keywords

bicarbonate, lactic acidosis, shock

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Introduction

The use of sodium bicarbonate for the treatment of severe lactic acidosis continues to generate intense debate [1,2]. Bicarbonate therapy is still used when intensive care practitioners are faced with patients whose pH falls below 7.20, while in a recent North American survey over two-thirds of practitioners use this treatment when they faced patients with pH below 7.00 [3]. The 2008 update of the Surviving Sepsis guidelines suggests that 'no evidence supports the use of bicarbonate therapy in the treatment of hypoperfusion-induced lactic acidosis associated with sepsis' and recommend against the use of sodium bicarbonate in those patients with pH at least 7.15 [4••]. The evidence for this recommendation is suggested to be 1B, a strong suggestion based upon the moderate quality evidence. Is this a reasonable conclusion based on the available evidence, and what of those patients whose pH is below 7.15? Here, we review the issue of bicarbonate therapy for lactic acidosis. Surprisingly, there are no large randomized controlled clinical trials upon which to base recommendations.

Mechanistic cause of lactic acidosis

In clinical practice, particularly in critically ill patients, lactic acidosis is essentially always an adverse finding. Elevated lactate in these patients generally results from a combination of increased production (also known as type A lactic acidosis) and impaired clearance (type B lactic acidosis). Lactic acid is produced as a byproduct of glycolysis when the rate of oxidative phosphorylation is insufficient to fully take up pyruvate produced as the final step of glycolysis. The ability of oxidative phosphorylation to metabolize pyruvate depends on the availability of oxygen to act as a sink for electrons produced at the end of the electron transport chain.

As oxygen delivery and utilization are fundamental to normal metabolism of glucose, pyruvate and lactate, disruption of any part of oxygen transport can result in excess lactate production. Inadequate total body oxygen delivery defines shock, whether hypovolemic, cardiogenic, distributive, obstructive – or most commonly, a combination of these entities. Regional ischemia before

onset of shock, such as mesenteric ischemia, limb compartment syndromes, or other types of arterial insufficiency, is also an important cause of lactic acidosis in critically ill patients. Thus, the finding of lactic acidosis without overt shock should prompt a search for a regional source. Severe anemia and drugs or toxins, which can interfere with oxidative phosphorylation such as metformin, propofol, ASA and carbon monoxide are also occasionally responsible for increased lactate production.

Lactate clearance has been well characterized, with metabolism to pyruvate in the liver responsible for over 50% of the clearance [5,6], while the kidney and to a lesser extent skeletal muscle, red blood cells and the heart metabolize the remainder. Due to resorption in the proximal convoluted tubule, urinary excretion of lactate is normally under 2%, rising to at least 10% with markedly elevated lactate levels [7]. While lactate clearance in healthy individuals is well understood, the mechanism behind impaired clearance in critically ill patients remains only partly defined. When confronted with hypoperfusion resulting in outright organ dysfunction such as 'shock liver', impaired hepatic clearance is easily attributable to the hepatic manifestation of global organ impairment. However, lactic acidosis can occur in patients who are hemodynamically normal but suffering from systemic inflammatory states such as early sepsis. It appears as though circulating inflammatory mediators change the liver from an organ which extracts lactate to one which actually produces excess lactate [8,9].

Hydrogen ion (H⁺) regulation

Internal homeostasis is fundamental for maintaining life, so significant deviations from normal biochemical concentrations of electrolytes and other molecules generally indicate a physiologically important abnormality in homeostatic function. Hydrogen ion concentration is particularly tightly regulated both intracellularly and extracellularly. Normal hydrogen ion concentration is approximately 40 nmol/l. Interestingly, the life sciences have adopted the practice of expressing hydrogen ion concentration as $-\log_{10}([H^+]) = \text{pH}$ from the physical sciences in which hydrogen ion concentrations vary so dramatically that a logarithmic scale was required. This has the effect of obscuring the extent of deviations from normal. For example, a change in pH from a normal value of 7.4 to 7.2 results in a 60% increase in hydrogen ion concentration from 40 to 63 nmol/l and a further increase to 100 nmol/l at a pH of 7.0.

When we consider other tightly regulated cation concentrations such as Na⁺ or K⁺, this H⁺ ion concentration increase is substantial. Changes in ion concentrations depend upon the flux in to and out of the volume of distribution of the ion and, importantly, the size of the volume of distribution. As a result, Na⁺ concentrations can

change only slowly. For example, infusion of 250 ml of 3% saline over 1 h (a very high Na⁺ flux) will contribute ~80 mEq compared with a total body pool of typically ~6000 mEq (140 mEq/l × 60% × body weight) so that Na⁺ concentration changes only slightly. Thus, Na⁺ concentrations depend on the large size of total body Na⁺ and water pools, and only very marginally on hourly or daily Na⁺ or water fluxes through these pools. When Na⁺ concentration is abnormal, is the problem with Na⁺ flux or Na⁺ or water pools? Clearly, it is a problem with the Na⁺ or water pools.

In contrast the H⁺ pool of 40 nmol/l in the extracellular space and approximately the same concentration in the intracellular space totals less than 0.01 mEq. Extensive extracellular and intracellular buffer systems increase the effective H⁺ pool substantially to about 1000 mEq. In comparison, the flux of H⁺ through this pool of normal health is high (see below) and can easily increase 10-fold during stress and muscle exertion. Thus, production and clearance of H⁺ become dominant mechanisms of regulation. When H⁺ concentration is abnormal, is the problem with H⁺ flux or H⁺ and buffer pools? In acidoses that are stable over days and weeks, the problem may be with the buffer pool but in lactic acidosis due to shock the problem is clearly with H⁺ flux.

H⁺ titrated by bicarbonate administration: in context

The primary source of H⁺ production is simply metabolism. For example, approximately 200 ml of CO₂ is produced per minute by a typical human, which is the same amount of CO₂ produced by bicarbonate buffering of 9 mEq H⁺ per minute or 540 mEq H⁺ per hour. For higher metabolic rates (which can increase 10-fold or more), the effective rate of acid production increases proportionately. For anaerobic metabolism, this same acid flux no longer is manifest solely as CO₂ production but is also converted into lactic acid production, where clinicians consider bicarbonate administration to increase the buffer pool size.

The problem is not in the buffer pool size. The buffer pool size is overwhelmed by the H⁺ flux in to the pool. The 50 mEq per ampule of bicarbonate is small in comparison to the H⁺ flux in to the pool. Thus, in the context of the magnitude of the acid flux that is associated with metabolism (hundreds of mEq per hour), it is clear that use of buffers will never keep up and, ultimately, always fails unless aerobic metabolism is restored.

Distinguishing acidosis due to increased H⁺ flux from decreased buffer pool size

Low extracellular bicarbonate concentrations may be due to the titration of bicarbonate by a new acid (increased

H⁺ flux) or by loss of bicarbonate rich fluid from the extracellular compartment so that the buffer pool is reduced. A simple way to distinguish between these two possibilities is to calculate the anion gap as $\text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)$, which is elevated when the cause is titration of bicarbonate by a new acid. Approaches using the Stewart strong ion difference can also be used and are more accurate, although the increase in accuracy is often not necessary in the clinical setting to arrive at a reasonable working answer to the distinction between these two main possibilities.

Potential benefits of bicarbonate administration: not relevant to lactic acidosis

Administration of bicarbonate (or equivalent such as a metabolic precursor like citrate) to treat loss of bicarbonate from the buffer pool, for example, during renal tubular acidosis, has a long history of success. For example, one easily observed physiologic consequence of extracellular acidosis is the increase in respiratory drive, increase in respiratory rate, and the potentially uncomfortable increase in work of breathing. This is readily and safely treated by administration of bicarbonate (or equivalent) over days or weeks, to replace losses due to renal tubular acidosis. Thus, the use of bicarbonate administration to treat and reduce the adverse consequence of increased respiratory drive can be helpful in the setting of a relatively stable acidemia due to bicarbonate loss from the buffer pool.

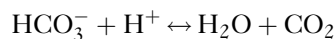
This reasoning does not translate to the clinical setting of lactic acidosis due to shock or tissue hypoperfusion. As indicated above, the problem during lactic acidosis is not a problem with buffer pool size but, rather, a problem with handling very high acid flux arising from metabolism.

Why changing extracellular pH is often not effective

The source of lactic acid during shock is intracellular. Only when it diffuses out of cells and enters the extracellular compartment is it manifest as increased plasma lactate levels. The primary problem is not in the extracellular compartment. Thus, an outside-in therapeutic strategy does not directly address the inside-out problem of lactic acidosis due to shock. The next problem is that the intracellular compartment, in which improved pH is hoped to have a beneficial effect on cell and organ function, is not readily accessible to extracellular H⁺ and HCO₃⁻ ions. Cellular membranes prevent easy flux. Thus, bicarbonate administration, which increases extracellular pH does not readily correct intracellular acidosis and therefore organ function, for example, left ventricular contractility, does not improve much [10].

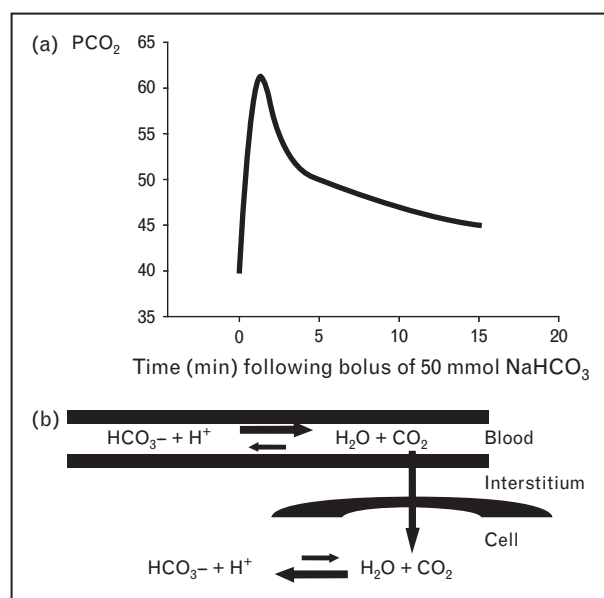
Intracellular acidosis due to bicarbonate administration

Administered bicarbonate reacts with acids to form water and CO₂.



While H⁺ and HCO₃⁻, as charged ions, do not readily diffuse across cell membranes, CO₂ does readily diffuse. In the intracellular compartment, the high CO₂ concentration will drive this same equation in reverse and generate intracellular H⁺ (Fig. 1 [10]). Thus, bicarbonate administration will cause intracellular acidosis unless P_{CO₂} can be controlled by increased ventilation. One ampule of bicarbonate fully reacted will generate over 1 l of CO₂. As normal CO₂ production is about one fifth of a liter per minute this means that one ampule of bicarbonate should be infused over 5 min or more if alveolar ventilation can be doubled – which is often challenging in a critically ill patient. Increasing alveolar ventilation up to five-fold to allow infusion of bicarbonate over 1 min is generally not possible. The practice of bolus infusion of an ampule of bicarbonate will result in mixing of the bicarbonate with a relatively small volume of blood, which will then have a very high local P_{CO₂}. When this volume of blood transits the lungs and heart and perfuses the coronary arteries, the cardiac myocytes will

Figure 1 Intracellular acidosis due to bicarbonate administration



(a) Blood chemistry alterations following bolus infusion of one ampule (50 mmol) of sodium bicarbonate in a patient whose initial pH is 7.00 [10,11]. (b) H⁺ and HCO₃⁻ are charged ions which do not readily diffuse across cell membranes, while CO₂ readily diffuses into the intracellular compartment resulting in generation of intracellular H⁺.

be transiently exposed to this very high local P_{CO_2} . This high P_{CO_2} will decrease myocardial contractility [11] and, in anecdotal animal experiments, can cause cardiac arrest.

Clinical evidence

To date, there have been only two small prospective randomized studies examining the role of sodium bicarbonate in lactic acidosis [10,12]. These two studies were similar in design, using individuals with lactic acidosis as their own controls, and randomizing the order in which they received either sodium bicarbonate or an equivalent amount of physiological saline. Taken together they enrolled 24 patients, and as both used this internal control methodology, neither could address any difference in morbidity or mortality between treatments. Their findings with respect to physiologic changes were similar, with sodium bicarbonate treatment resulting in substantial increases in arterial and venous pH, serum bicarbonate and partial pressure of carbon dioxide compared with physiological saline treatment (see Table 1 [10,12]). Additionally, sodium bicarbonate lowered plasma ionized calcium significantly compared with physiological saline. Despite the rather large difference in pH following treatment, no difference was detected with respect to cardiac output or mean arterial pressure. This held true even for patients with severe acidemia with pH less than 7.15 [10]. The increase in pH was transient so that much of the bicarbonate effect was gone after 30 min. As all patients were being treated with catecholamines, the observed lack of clinical sensitization following substantial reversal of the acidosis was puzzling, given good evidence that acidosis significantly attenuates the effect of catecholamines [13]. This led the authors to suggest that the 10% decrease in plasma ionized calcium countered any positive inotropic effect conferred from an increase in pH [10]. This hypothesis has yet to be tested clinically.

Thus, the available clinical trial data are limited to short-term physiological studies in critically ill human patients with moderate lactic acidosis. Despite their limitations, these trials demonstrate a remarkable lack of sustained effect. Concordance of these results with the above consideration of acid–base physiology suggests that an adequately powered randomized controlled trial of bicarbonate administration for lactic acidosis would not likely find improvement in 28-day mortality or other

clinically significant endpoints. As reflected by current clinical practice [3], once the metabolic derangement results in a pH below 7.0, critical care practitioners often perceive that they have run out of other treatment options and the majority choose to treat with sodium bicarbonate. In view of the paucity of data, we are not able to agree or disagree with this approach. However, given earlier considerations of the pathophysiology of lactic acidosis due to shock, it is clear that reversal of shock and the underlying cause of shock are paramount.

Potential new therapies

Continuous renal replacement therapy (CRRT) has become common therapy in the intensive care unit, with many centers initiating CRRT early in the course of renal impairment in hemodynamically unstable patients. Most patients who have lactic acidosis as a result of shock will also exhibit renal impairment, and the acidosis resulting from both causes is often severe enough that acute dialysis is warranted for refractory metabolic acidosis rather than volume overload or hyperkalemia. In this setting, it is important to carefully consider the choice of replacement fluid. Although in septic patients, regional anticoagulation using an isotonic citrate solution seems to prolong filter life, using this solution in those with severe metabolic acidosis may be hazardous as it appears that citrate increases the strong ion gap, decreasing bicarbonate and pH [14]. Furthermore, the belief that CRRT can adequately clear lactate depends heavily on the rate of lactate production versus the extracorporeal blood flow and convective clearance rate. Our anecdotal experience is that an inability to meet standard resuscitation goals such as a mean arterial pressure of at least 65 mmHg combined with central venous saturation at least 70% [4**] is highly correlated with refractory acidemia and poor lactate clearance despite aggressive CRRT. In agreement with this is a recent case report of severe metformin-induced lactic acidosis requiring not one but two simultaneous high-flow continuous veno-venous hemofiltration (CVVH) runs to clear lactate [15]. This underscores that the main treatment in treatment of lactic acidosis is to reverse the cause of lactate accumulation rather than treat the metabolic consequence.

Other buffers such as carbicarb [1:1 mix of disodium carbonate and sodium bicarbonate and tris-hydroxymethyl aminomethane (THAM)] that neutralize acid without the generation of CO_2 , have been suggested and tried [16,17]. Uniformly, no clinically important benefits have been demonstrated. Once again, consideration of the underlying acid–base physiology and the magnitude of the endogenous H^+ flux in comparison with the comparatively miniscule buffering dose may explain these negative results.

Table 1 Change in blood chemistry 15 min following 2 mmol/kg bicarbonate infusion [10]

pH	+0.14
HCO_3^-	+6 mmol/l
CO_2	+5 mmHg
Plasma ionized calcium	−0.08 mmol/l

Conclusion

In summary, we find the available evidence suggests that sodium bicarbonate in doses of 1–2 mEq/kg does significantly raise the pH and serum bicarbonate as well as the partial pressure of carbon dioxide, although this effect is transient. This does not translate into improved hemodynamics or augmented sensitivity to catecholamines, possibly due to a decrease in serum ionized calcium levels. Thus, we agree with the recommendation of the 2008 Surviving Sepsis guidelines that sodium bicarbonate not be given at pH greater than 7.15. Indeed, we do not think that bicarbonate administration is indicated for lactic acidosis due to shock for pH above 7.0. Should bicarbonate be used, consideration must be given to slow infusion and a plan for clearing the CO₂ that is produced and measuring and correcting ionized calcium as the resultant 10% drop may decrease cardiac and vascular contractility and responsiveness to catecholamines. When CRRT is used during severe acidosis, we recommend bicarbonate-based replacement fluid over citrate as citrate may increase the strong ion gap. Effective therapy of lactic acidosis due to shock is to reverse the cause.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 466).

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