Review

Bench-to-bedside review: Treating acid–base abnormalities in the intensive care unit – the role of buffers

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Abstract

The recognition and management of acid–base disorders is a commonplace activity for intensivists. Despite the frequency with which non-bicarbonate-losing forms of metabolic acidosis such as lactic acidosis occurs in critically ill patients, treatment is controversial. This article describes the properties of several buffering agents and reviews the evidence for their clinical efficacy. The evidence supporting and refuting attempts to correct arterial pH through the administration of currently available buffers is presented.

Keywords acid-base, acidosis, bicarbonate, buffer, tromethamine

Introduction

Acidemia occurs commonly in critically ill patients. Certain acidoses have specific remedies, for example insulin for the patient with diabetic ketoacidosis, or fomepizole for the treatment of methanol intoxication. However, the optimal management of other forms of acidosis, such as lactic acidosis from sepsis, is controversial. Specifically, it is unclear for many of these disorders whether it is appropriate to attempt to correct arterial pH through the administration of sodium bicarbonate or other 'buffering' agents, while efforts to treat the underlying cause of the acidosis proceed apace. Similarly, whether pH should be corrected in patients with hypercapnea as a result of lung protective strategies of mechanical ventilation is unknown. Herein we describe the properties of several buffering agents and review the evidence for their clinical efficacy. We do not discuss the administration of sodium bicarbonate to patients with bicarbonate-losing metabolic acidoses such as occurs with diarrhea or renal tubular acidosis – a practice that enjoys widespread acceptance. Similarly, the role of buffering agents in treating intoxication is beyond the scope of the present review.

What is the harm associated with low pH?

Because we understand poorly both the effects of an elevated arterial H+ concentration ($[H^+]$) as well as the effects of attempting to correct it, deciding whether to administer a buffering agent such as sodium bicarbonate to patients with non-bicarbonate-losing forms of metabolic acidosis is difficult. Proponents of such an approach typically argue along the following lines [1].

- An elevated arterial $[H^+]$, in and of itself, is harmful.
- The administration of buffer X intravenously will lower the arterial $[H^+]$.
- Lowering the $[H^+]$ with buffer X confers clinical benefit.
- Any adverse effects of buffer X will be outweighed by its benefit.

We first consider the evidence supporting the first assertion. The remaining ones are discussed below in the context of each individual agent.

What are the effects of an elevated [H+]?

Because protein function is sensitive to the $[H^+]$ of its environment, an increase in arterial $[H^+]$ might be expected to have important detrimental effects on a host of bodily functions. However, it is unclear to what extent the arterial blood pH reflects the intracellular pH, which seems likely to be more relevant. By way of example, consider the effect of decreasing blood flow to a tissue by 50%. According to the

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ALI = acute lung injury; ARDS = acute respiratory distress syndrome; $[A_{tot}]$ = total concentration of weak acids; $[H^+]$ = H+ concentration; Pco_2 = partial CO_2 tension; [SID] = strong ion difference; THAM = tris-hydroxymethyl aminomethane.

Fick relationship the arterial–venous partial CO_2 tension (PCO_2) difference will double, assuming that local CO_2 production is constant. This will have the effect of raising the tissue PCO_2 and lowering its pH; however, the arterial PCO_2 and pH are unchanged and hence do not reveal the abnormality. The meaning of an individual arterial blood pH is further limited when one considers the diversity of micro-circulations and tissue metabolisms throughout the body. The effects of the elevated [H+] may also be difficult to separate from the effects of the accompanying anion; lactate buffered to a pH of 7.4, for example, causes a decrease in cardiac contractility in animal models [2]. Finally, discerning the effect of an elevated [H+] from that of the underlying process causing the acidosis – hypoperfusion, sepsis, or diabetic ketoacidosis for example – is difficult.

Nevertheless, lowering the arterial pH has rather convincingly been shown to cause a decrease in cardiac contractility. This effect has been demonstrated in isolated [3,4] and whole animal heart preparations [5,6], as well as in excised human ventricular muscle [7]. The net influence of acidosis on the cardiovascular system is complicated, however, by concomitant stimulation of the sympathetic–adrenal axis. As a result, acidemia has been shown to increase cardiac output and pulmonary artery pressure, whereas pulmonary vascular resistance is not changed [8]. The responsiveness of adre-nergic receptors to circulating catecholamines is decreased [9–11], and the load tolerance of the right ventricle is reduced [12]. It is unclear whether resuscitability from induced ventricular fibrillation is impaired [13–15]. Fewer patients with an arterial pH below 7.1 have been studied, making it difficult to draw any conclusions. Both respiratory and metabolic acidoses appear to have similar effects, although the effects of respiratory acidosis are more rapid, presumably because of rapid diffusion of CO_2 across cell membranes.

Acute hypercapnea causes a decrease in diaphragmatic contractility and endurance time [16], along with an increase in cerebral blood flow. In fact, acute elevation in PCO_2 to more than 70 mmHg may cause loss of consciousness and seizures [17]. In contrast, more gradual elevations in PCO_2 are well tolerated, as exhibited by patients with chronic obstructive pulmonary disease. Broad clinical experience with the application of lung protective strategies of mechanical ventilation in patients with acute lung injury (ALI) and status asthmaticus suggests that modest acidemia (typically pH 7.15–7.30, PCO_2 50–70 mmHg) is remarkably well tolerated. In general, patients with so-called permissive hypercapnea have a decrease in systemic vascular resistance, an increase in heart rate, cardiac output, oxygen delivery, mean pulmonary artery pressure, and mixed venous oxygen saturation, and unchanged mean arterial pressure and pulmonary vascular resistance.

The effects of acidosis may differ according to type and magnitude. Disparate effects of three types of extracellular acidosis – inorganic, respiratory, and lactic – on left ventricular function in isolated rabbit hearts have been described [18]. Lactic acidosis caused a significant increase in the time to peak left ventricular pressure while retarding ventricular relaxation, reinforcing the concept that lactate ions have an independent effect on myocardial function. Different types and severity of acidosis may also induce different patterns of inflammatory response. For example, murine macrophage-like cells stimulated with lipopolysaccharide exhibited an essentially proinflammatory response when the media contained hydrochloric acid, but an anti-inflammatory response when the media contained lactic acid [19]. Furthermore, hydrochloric acid infusion decreased the blood pressure in septic rats in a dose dependent manner, but whereas rats with moderately severe acidosis (standard base excess of 5–10 mEq/l) had increased plasma nitrate/nitrite levels, rats with severe acidosis did not [20].

Are there beneficial effects to an elevation in [H+] in critical illness?

Interesting data are emerging regarding potential protective effects of acidosis, particularly hypercapnic acidosis, in various experimental models. Acidosis has been shown to protect cells in a variety of organs (heart, lung, brain, and liver) against injury from a number of insults, including hypoxia [21–25]. In contrast, hypocapnic alkalosis worsened ischemia–reperfusion ALI in isolated rabbit lungs [26], whereas hypercapnic and metabolic acidosis afforded protection [27]. Buffering the hypercapnic acidosis attenuated the protection conferred. Similarly, rabbits ventilated with injurious tidal volumes exhibited less ALI histologically when hypercapnea was present [28]. A protective effect of hypercapnea on the development of ALI has also been demonstrated for an experimental model of extrapulmonary ALI in which rats were subjected to splanchnic ischemia–reperfusion injury [29]. Hypercapnic acidosis was effective at attenuating endotoxin-induced ALI in an *in vivo* rat model [30]; in fact, both prophylactic and therapeutic hypercapnic acidosis ameliorated lung injury. Conceivably, reducing cells' mechanical work (e.g. in cardiac cells) and metabolic demand during hypoxia may protect them from ischemia.

Interestingly, the ARDS Network trial [31], which demonstrated reduced mortality in ALI and acute respiratory distress syndrome (ARDS) using a protocol employing low tidal ventilation, allowed for sodium bicarbonate infusion for acidemia. Whether this therapy had any effect, either negative or positive, on patient outcome is unclear.

In summary, the negative impact of an elevated arterial [H+] is frequently difficult to discern. We consider the evidence for and against the administration of different buffering agents within the context of each agent below.

Buffering agents

Buffers have conventionally been defined in acid–base chemistry as substances that allow a solution to 'resist'

changes in pH in response to administration of H^+. Problems exist with this definition, however. First, as discussed below, conventionally defined buffers such as $NaHCO_3^-$ may cause an increase in arterial $[H^+]$ in certain circumstances when they are administered intravenously, while Stewart [32] demonstrated that a solution containing weak acids (buffers) – such as blood containing albumin – 'resists' changes in $[H^+]$ much less effectively than the same solution without any weak acid. Also, the use of the term 'buffer' obscures the unique mechanisms of each agent. Nevertheless, because of its widespread use, we employ the term buffer to refer to any agent whose intent is to raise the arterial pH when given intravenously.

Sodium bicarbonate

Does sodium bicarbonate lower the arterial [H^+]?

The effects of sodium bicarbonate infusion can be understood within the following context. Although the Henderson equation ($[H^+] = 24 \times P_{CO_2}/[HCO_3^-]$) accurately describes the dissociation equilibrium for carbonic acid, it is misleading to assume that $[HCO_3^-]$ is an independent determinant of $[H^+]$. In fact, the independent determinants of $[H^+]$ in the blood are the strong ion difference [SID], the total concentration of weak acids $[A_{tot}]$, and the P_{CO_2} [32]. Weak acids $[A_{tot}]$ include substances such as albumin and PO_4^-, change relatively little acutely, and have little impact on $[H^+]$. Strong ions are those that dissociate fully (or nearly so) in aqueous solutions, such as Na^+ and Cl^-. Because they are fully dissociated, strong ions do not participate in chemical reactions in blood like weak ions (such as H^+ or HCO_3^-) do. Because they do not react chemically, all that matters (for acid–base purposes) is the net difference in their charges.

The [SID] is defined as the difference between the sum of the major cations (Na^+, K^+, Ca^{2+}, Mg^{2+}) and the sum of the major anions (Cl^-, SO_4^-, lactate) in the blood. [SID] is so important because the difference in charges affects how much water will dissociate into the charged species H^+ and OH^- (i.e. [SID] is the major determinant of pH).

The arterial $[HCO_3^-]$ and pH depend simply and quite inextricably on the [SID], $[A_{tot}]$, and P_{CO_2}. The intravenous infusion of sodium bicarbonate solution typically lowers arterial $[H^+]$ (raising the pH) through an increase in [SID]. This occurs because Na^+ is a strong cation whereas HCO_3^- is not, but rather reacts with $[H^+]$ to create CO_2. When ventilation is not limited, the excess CO_2 that is produced can be eliminated, and arterial pH is increased so that most [5,33–36], but not all [37,38], whole animal studies have shown an increase in arterial pH when sodium bicarbonate is administered. Additionally, two prospective, randomized controlled trials conducted in mechanically ventilated patients with lactic acidosis [39,40] demonstrated that sodium bicarbonate given intravenously causes a modest increase in arterial pH. When ventilation is fixed, however, as commonly occurs in mechanically ventilated patients, the effect of

sodium bicarbonate may be to lower arterial pH, as was seen in patients ventilated with a lung protective strategy [41].

However, evidence supporting an increase in arterial pH with bicarbonate infusion does not alone support its use for the treatment of acidosis. First, bicarbonate infusion has been shown to stimulate the production of lactate in animal models of hypoxic lactic acidosis [34,38], phenformin-induced lactic acidosis [37], hemorrhagic shock [35], and diabetic keto-acidosis [36,42]. As mentioned above, lactate is itself a strong anion, which may have independent negative effects on cardiac contractility [2]. Furthermore, the effects of bicarbonate administration on intracellular pH are far from clear. Because CO_2 diffuses readily across cell membranes, sodium bicarbonate administration may cause a decrease in intracellular pH. In fact, the findings of cellular and whole animal model studies examining the effects of bicarbonate infusion on intracellular pH are variable, with intracellular $[H^+]$ rising [36], falling [37,38,43–48], not changing [4,14,34,35], or either rising or falling depending on the buffer used [49,50]. Two studies of normal volunteers using very different experimental designs have investigated the effect of bicarbonate on intracellular pH using magnetic resonance spectroscopy. In one study [51] bicarbonate attenuated the decrease in intracellular muscle pH during exercise induced metabolic acidosis while raising the arterial pH and P_{CO_2}. In the other study [46] sodium bicarbonate caused a fall in brain pH.

The effect of bicarbonate on intracellular pH may depend on the extracellular nonbicarbonate buffering capacity [52]. In this model, bicarbonate reacts with H^+ to form H_2O and CO_2 (reaction 1). The abrupt decrease in $[H^+]$ caused by reaction 1 causes the dissociation of $[H^+]$ from nonbicarbonate buffer (back titration of the buffer), which in turn reacts with bicarbonate to produce more CO_2. Finally, the CO_2 diffuses readily into cells, decreasing intracellular pH (an effect that may be minimized by intracellular bicarbonate buffer).

Does sodium bicarbonate confer any beneficial effects?

In general, whole animal studies fail to demonstrate any hemodynamic benefit of sodium bicarbonate therapy over isotonic saline [5,33,34,37,38,53,54]. Additionally, two randomized controlled trials of sodium bicarbonate therapy in patients with lactic acidosis [39,40] found no benefit from this therapy over sodium chloride in improving global hemodynamics or the cardiovascular response to infused catecholamines.

The effects of sodium bicarbonate therapy in patients with permissive hypercapnea have received little study, notwithstanding the inclusion of sodium bicarbonate in the aforementioned ARDS Network low tidal volume protocol [31]. One small, uncontrolled study of patients receiving lung protective ventilation for ALI showed a decrease in arterial pH with bicarbonate therapy [41]. No benefit from sodium bicarbonate has been found in the management of diabetic ketoacidosis [55,56].

Summary

Intravenous sodium bicarbonate may decrease the arterial [H^+] when ventilation is not limited, but its effect on intracellular pH is unclear. Perhaps more importantly, no clinical benefit from sodium bicarbonate has been demonstrated in the setting of lactic or ketoacidosis, but volume overload, hyperosmolarity [57], and a decrease in ionized calcium [40] are known to complicate its use.

Carbicarb

Carbicarb is an equimolar mixture of sodium bicarbonate and sodium carbonate that is not currently available clinically. Carbicarb raises the [SID] (lowering the arterial [H^+]) far more [33,34,43,58] and boosts the P_{CO_2} far less [33,34,45] than does sodium bicarbonate when given intravenously to animals with metabolic acidosis. If the inability of sodium bicarbonate to demonstrate a benefit in patients with non-bicarbonate-wasting forms of metabolic acidosis is due to increased CO_2 generation, then carbicarb should be a superior agent. In fact, although carbicarb more consistently lowers intracellular [H^+] [34,43,45], studies of its effects on hemodynamics have yielded conflicting findings [4,33,34,43]. This agent deserves further study.

Tromethamine

Tris-hydroxymethyl aminomethane (THAM) is a weak alkali (pK = 7.8) that reduces arterial [H^+] without producing CO_2. Because it penetrates cells easily, it also reduces intracellular [H^+]. Protonated THAM is excreted by the kidneys.

Although THAM has been commercially available for some time and has seen considerable use outside North America, there are few studies of its efficacy. THAM incompletely buffered metabolic acidosis but significantly improved contractility and relaxation in an isolated blood perfused rabbit heart model [59]. The combination of THAM and sodium bicarbonate perfectly buffered acidosis without modifying CO_2, resulting in a significant improvement in contractility. Weber and colleagues [60] studied the effect of THAM on systemic hemodynamics in 12 patients with ARDS in whom permissive hypercapnea was induced with a target CO_2 of 80 mmHg. Hypercapnea had the following effects on hemodynamics in control patients, in whom no attempt was made to correct the pH: reduced systemic vascular resistance, mean arterial pressure and myocardial contractility, and increased cardiac output and pulmonary artery pressure. Patients who received THAM experienced significantly less myocardial depression when compared with control patients, whereas the effects of hypercapnea on mean arterial pressure and mean pulmonary artery pressure were ameliorated. Administration of THAM to 10 patients with acidosis and ALI caused significant improvements in arterial pH and base deficit, as well as a decrease in CO_2 that was not adequately explained by the effects of ventilation [41].

Whether it is even desirable to 'buffer' hypercapnea in ALI and hypoperfusion states is unclear, as discussed above.

THAM also has potentially serious side effects, including hypoglycemia, hyperkalemia, extravasation related necrosis, and, in neonates, hepatic necrosis [61]. Nevertheless, THAM is an interesting agent that deserves further study, including as a potential therapy for patients with lactic acidosis.

Alternative agents for lactic acidosis

Dichloroacetate

Conceivably, the lactic acidosis of sepsis may be due in part to impaired pyruvate oxidation. The pyruvate dehydrogenase complex is a key regulator of carbohydrate metabolism. This complex is inactivated by a pyruvate dehydrogenase kinase that may be activated by sepsis [62], leading to pyruvate accumulation and subsequently an increase in lactate. Dichloroacetate stimulates pyruvate kinase, increasing the oxidation of pyruvate to acetyl coenzyme A.

Initial studies of dichloroacetate in animals and humans were indeed promising, demonstrating that dichloroacetate effectively reduced arterial [H^+] and lactate levels [63–65]. There has been one large, randomized, placebo-controlled trial of dichloroacetate in patients with lactic acidosis due to sepsis, cardiogenic shock, or massive hemorrhage. Although dichloroacetate reduced the arterial blood lactate concentration and improved the arterial pH, it had no effect on hemodynamics or survival [66]. Further studies of dichloroacetate in other patient populations and using different dosing schedules are warranted. Currently, this therapy is investigational.

Thiamine

Patients with lactic acidosis due to thiamine deficiency (beri beri) may respond promptly to its administration. Patients at risk include those with chronic alcoholism, malignancy, chronic illness, and short bowel syndrome. Lactic acidosis may also develop in HIV infected patients receiving nucleoside analog reverse transcriptase inhibitors [67]. This disorder is thought to represent drug induced mitochondrial dysfunction, and there are anecdotal reports of improvement with thiamine [68]. Although thiamine is an essential cofactor for pyruvate dehydrogenase, its utility in sepsis with lactic acidosis has not been studied.

Volume expanders and acid–base disorders

Considerable debate exists regarding the relative merits of sodium chloride, lactated Ringer's solution, or various colloid solutions in the resuscitation of patients in shock. The different chemical compositions of these fluids translate into different acid–base consequences. For example, infusing large volumes of normal saline intravenously lowers the [SID] (because the [SID] of saline is zero), raising [H^+] (and lowering pH). Whether the 'dilutional acidosis' that results is harmful, inconsequential, or even protective to the patient is unclear. Lactated Ringer's solution also has an [SID] of zero but, because lactate is metabolized in the liver (assuming adequate hepatic perfusion and function), the effect is similar

to infusing a fluid with a positive [SID]. Whether this might be advantageous is not known. New formulations of colloids have been investigated; in an animal model of septic shock, volume expansion with Hextend (Bio Time, Inc., Berkeley, CA, USA) – a synthetic colloid in a balanced electrolyte solution that does not produce metabolic acidosis in humans – conferred longer survival when compared with 0.9% normal saline [69].

Conceivably, the differing effects of various volume expanders on acid–base status may be important clinically, but it is the authors' view that considerably more work remains to be done in this area before volume expanders other than normal saline can be recommended. A detailed analysis of this subject is beyond the scope of the present review.

When should I administer a buffering agent?

The lack of evidence supporting buffer therapy in human acidosis makes it difficult to provide explicit recommendations. Currently, it is unclear whether it is ever advantageous to administer a buffering agent to a patient with lactic acidosis or ketoacidosis. In fact, we do not recommend administration of sodium bicarbonate to patients with lactic acidosis, regardless of the pH. This includes lactic acidosis caused by hypoperfusion, sepsis, mitochondrial dysfunction, or liver failure, or in the setting of cardiopulmonary bypass. If the decision is made to administer sodium bicarbonate, then slow infusion is preferable and objective measures of benefit (or harm) should be sought. Further study into the efficacy of alternative buffering agents such as THAM and carbicarb is merited.

In patients with severe hyperchloremic metabolic acidosis from diarrhea or renal tubular acidosis, the administration of sodium bicarbonate is reasonable. Whether a patient will benefit from this therapy is difficult to predict and probably depends on the clinical circumstance. Patients with critical respiratory compromise, who cannot easily compensate for acidemia, could also benefit. Nevertheless, we find these patients to be quite rare. In the much more common circumstance of modest hyperchloremic acidosis, attempting treatment with buffers is unlikely to be helpful and may serve to distract the clinician from addressing the underlying problem.

When buffer therapy is given its effect can be monitored by serial determination of arterial blood pH, P_{CO_2}, and serum anion gap corrected for albumin concentration. Failure to correct for the nearly ubiquitous hypoalbuminemia present in the critically ill introduces a systematic error in the detection of unidentified anions such as lactate or ketoacids [70]. An alternative approach is to calculate the strong ion gap, but this requires measurement of albumin and phosphate concentrations as well as a little more mathematics, and this may be too cumbersome for regular clinical use.

Conclusion

Acidemia has both harmful and beneficial biological effects. Sodium bicarbonate is generally ineffective in raising pH

when ventilation is limited, as in patients with ARDS. Even when alkalinizing agents can correct the pH, evidence of efficacy is lacking. Thus, these treatments should not be considered standard therapy in patients with organic acidoses, such as lactic acidosis. Rather, attention should be directed toward correcting the underlying basis for the acidosis. Alternative buffer agents, such as tromethamine, offer potential advantages over sodium bicarbonate, but clinical trials in humans are lacking.

Competing interests

None declared.

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