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REVIEW ARTICLE

Metabolic acidosis in childhood: why, when and how to treat

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Abstract

Objectives: To critically discuss the treatment of metabolic acidosis and the main mechanisms of disease associated with this disorder; and to describe controversial aspects related to the risks and benefits of using sodium bicarbonate and other therapies.

Sources: Review of PubMed/MEDLINE, LILACS and Cochrane Library databases for articles published between 1996 and 2006 using the following keywords: metabolic acidosis, lactic acidosis, ketoacidosis, diabetic ketoacidosis, cardiopulmonary resuscitation, sodium bicarbonate, treatment. Classical publications concerning the topic were also reviewed. The most recent and representative were selected, with emphasis on consensus statements and guidelines.

Summary of the findings: There is no evidence of benefits resulting from the use of sodium bicarbonate for the hemodynamic status, clinical outcome, morbidity and mortality in high anion gap metabolic acidosis associated with lactic acidosis, diabetic ketoacidosis and cardiopulmonary resuscitation. Therefore, the routine use of sodium bicarbonate is not indicated. Potential side effects must be taken into consideration. Treating the underlying disease is essential to reverse the process. The efficacy of other alternative therapies has not been demonstrated in large-scale studies.

Conclusions: Despite the known effects of acidemia on the organism in critical situations, a protective role of acidemia in hypoxic cells and the risk of alkalemia secondary to drug interventions are being considered. There is consensus regarding the advantages of alkali and sodium bicarbonate therapy in cases with normal anion gap; however, in the presence of high anion gap acidosis, especially lactic acidosis, diabetic acidosis and cardiopulmonary resuscitation, the use of sodium bicarbonate is not beneficial and has potential adverse effects, limiting its indication. The only points of agreement in the literature refer to the early treatment of the underlying disease and the mechanisms generating metabolic acidemia. Other promising treatment alternatives have been proposed; however, the side effects and absence of controlled studies with pediatric populations translate into lack of evidence to support the routine use of such treatments.

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Introduction

Acid-base disorders (ABD) are frequently observed in pediatric intensive care. Among them, metabolic acidosis (MAC) is usually associated with primary diseases or occurs as a result of secondary complications in critically ill patients. Severe acidemia is recognized as a highly morbid and lethal condition, with earlier, classical analyses indicating immediate treatment with alkali, regardless of the method used to determine the pathophysiological mechanism of acidosis.

The arguments favoring treatment with buffer agents are based on the deleterious action of high plasma concentrations of H^+, reducing pH. The administration of sodium bicarbonate (SB) would in theory interrupt the metabolic disturbances associated with acidemia, promoting benefits that compensate for treatment-induced adverse effects. Nevertheless, many reports reveal that SB may fail to increase plasma pH under certain circumstances, in addition to promoting intracellular acidosis, among other undesirable effects.[1-5] In addition, a cytoprotective effect of acidemia has been reported, which could be harmed by the alkalinizing action of SB.[4]

It is well-known and accepted that pathologic conditions such as diarrhea or renal tubular acidosis, in which acidosis results from primary loss of bicarbonate (normal anion gap), should be treated with exogenous bases such as SB.[4,6-9] However, there is controversy concerning the correction of acidemia using a standard and general formula across different diseases and clinical entities, especially those associated with high gap MAC, for which treatment with SB may not bring immediate benefits or change prognosis. This discussion is particularly valid for the use of SB in lactic acidemia (LA), diabetic ketoacidosis (DKA) and cardiopulmonary resuscitation (CPR).

These answers are still far from receiving a definitive answer. In clinical practice, different explanations are given for the pathophysiology of MAC. At the same time, new treatment alternatives are being proposed, with studies focusing on the side effects of drugs, in an attempt to replace SB with a safer drug. Other conditions associated with MAC, such as specific types of intoxication, inherited metabolic diseases, chronic renal failure, among others, will not be covered in this review. We will focus on the most current and relevant aspects related to the questions described above and the controversy regarding the use of SB in MAC, as well as on the treatment options currently under study.

Genesis and pathophysiology of metabolic acidosis and rational use of sodium bicarbonate

The logic of diagnosing ABD relies on the classical principles of acid-base balance (Henderson-Hasselbalch, Van Slyke and Siggaard-Anderson). In this context, the concept of anion gap, derived from the physicochemical principle of electroneutrality, is of interest, since it stratifies MAC into two types according to etiologic and pathophysiological mechanisms: MAC with high serum anion gap and normal chloride levels and MAC with normal serum anion gap and hyperchloremia (Table 1).[6,9,10] The main measured cation in the organism is Na^+, accounting for about 90% of positive charges. This means that unmeasured cations correspond to 10% of serum ions (by convention, K^+, Ca^{++} and Mg^{++} are unmeasured cations). Measured anions include HCO3- and Cl-, representing around 85% of negative charges. Thus, there is about 5% of unmeasured anions, exceeding the percentage of unmeasured cations for maintenance of normal electroneutrality (that is, unmeasured anions – unmeasured cations = 5% of serum ions). This 5% corresponds to 8-16 mEq/L (on average, 12±2 mEq/L), equivalent to a normal anion gap.[8,9] To make it simple:

- Measured anions + unmeasured anions = measured cations + unmeasured cations
- Unmeasured anions – unmeasured cations = measured cations – measured anions
- Anion gap = unmeasured anions – unmeasured cations
- Anion gap = measured cations – measured anions
- Anion gap = $Na^+ - (HCO3- + Cl^-)$ = 12±2 mEq/L

In MAC with high anion gap, there is primary addition or retention of acid charges (H^+) in the system, as occurs in LA, exogenous intoxications, renal insufficiency, DKA, etc. Thus, anion charges (unmeasured) must be increased for maintenance of electroneutrality, without need of changes in serum chloride.[6,8,10] A high anion gap reflects an increase of unmeasured anions (usually organic acids).

In the second scenario (normal anion gap and hyperchloremia), there is primary loss of bicarbonate (for example, diarrhea and tubular renal acidosis) without addition of acid charges. Since in this case there is no need to increase the sum of anion charges, the organism may compensate for electroneutrality by increasing chloride reabsorption in the renal tubule.

In almost all the situations of MAC with normal anion gap, that is, diseases with primary loss of bicarbonate, there is a general consensus regarding the administration of SB, following well-known clinical and laboratory standards, with the aim of avoiding an abrupt correction of blood bicarbonate levels and its harmful effects.[4,5,7-9]

However, the use of SB in other types of acidosis, especially those associated with high anion gap, such as sepsis-related LA, is controversial, with increasingly more evidence showing that the etiologic investigation and

treatment of the underlying condition is usually sufficient to reverse critical acidemia, without the need to use SB, as discussed below.

In the 1980s, Stewart described a new model of acid-base balance, whose principles were later reevaluated, ratified and enhanced by other authors.[11-16] Stewart's interpretation is based on principles such as electroneutrality, equilibrium dissociation and mass conservation, and on the identification of three independent variables that affect H^+ concentration in complex solutions such as plasma. These variables are:

1) Strong ion difference (SID), that is, the resulting balance between all the ions present in serum (strong cations – strong anions). Considering that some unmeasured ions may be present (such as sulfates and ketones), for practical effects the apparent SID is used (aSID), which is equivalent to the difference between the sum of all strong cations (Na^+, K^+, Mg^{++}, Ca^{++}) and the sum of all strong anions (Cl^- and others, such as lactate), usually measured in plasma.[13] In healthy individuals, this difference is around 40-42 mEq/L. To maintain serum electroneutrality, the remaining negative charges to balance this difference comprise especially CO_2 and weak acids (A^-), and less effectively OH^- ions. Strong ions (Na^+, K^+, Mg^{++}, Ca^{++}) are so called due to their trend to completely dissociate in aqueous solutions, as opposed to weak ions (albumin, phosphate and bicarbonate). In this approach, neither H^+ nor HCO_3^- are considered as strong ions. As the SID becomes more positive, $[H^+]$ (considered a weak cation) is reduced (with a consequent increase in pH) so that electroneutrality is maintained.[16]

   - aSID: $[Na^+ + K^+ + Mg^{++} + Ca^{++}] - [Cl^- + lactate^-]$

2) $PaCO_2$, an independent variable, may be altered by ventilation. The effects on $PaCO_2$ changes are well understood and produce the classical alterations expected for $[H^+]$.

3) Total concentration of non-volatile weak acids (A_{tot}): it is the total sum of weak acids ($AH + A^-$). Its value is flexible to ensure equilibrium with the other two variables and satisfy the principle of electroneutrality. Most weak acids (A^-) are proteins (mainly albumin) and phosphates.

The normal value of plasma A_{tot} has not been established, and the measurements performed have ranged between 12-24 mEq/L. In practical terms, A_{tot} can be estimated through total protein concentration or serum albumin,

where $[A^-]$ = 2.8 (albumin g/dL) + 0.6 (phosphate mg/dL) in pH = 7.4.

$A_{tot} = K_p \times [\text{total protein g/dL})$ or $A_{tot} = K_a \times [\text{albumin g/dL})$

Table 1 - Main causes of metabolic acidosis according to serum anion gap

High anion gap	Normal anion gap
Diabetic ketoacidosis	Diarrhea
Uremia and acute renal failure	Renal tubular acidosis
Lactic acidosis (types A and B): inborn errors of metabolism, shock, hypoxia, ischemia, etc. Lactic acidosis-D	Ureterosigmoidostomy Villous adenoma
Toxins (exogenous anions): methanol, ethylenglycol, salicylates, paraldehyde, formaldehyde, penicillin, carbenicillin, etc.	HypoaldosteronismUse of aldosterone inhibitors
Massive rhabdomyolysis	Uremia (initial stage)
Fasting ketosis	Increase in cations: K^+, Ca^{++}, Mg^{++} Cation retention: IgG, lithium
Hyperalbuminemia (transitory)	Hypoalbuminemia (low anion gap)
Late metabolic acidosis of the neonate	Some cases of diabetic ketoacidosis receiving insulin therapy

Source: Adapted from Halperin & Goldstein[9] and Rose.[10]

where K_p ranges from 2.43 to 3.88 and K_a ranges from 4.76 to 6.47.[12]

The approach by Stewart is based on the alteration of these independent variables. Parallel to the traditional approach, respiratory acidosis and alkalosis are related to independent variations in $PaCO_2$ (in this case, a change in plasma SID could occur as a compensatory response). MAC may result from a reduction in SID or increase in A_{tot}, whereas metabolic alkalosis would result from the opposite situation, a primary increase in SID or reduction in A_{tot} (Table 2).

Thus, changes in ABD cannot be seen as a consequence of bicarbonate concentration (this is merely a dependent variable). Therefore, the two possible sources of metabolic disturbances, that is, non-respiratory disturbances, would be SID or A_{tot}.

Also derived from Stewart's theory is the notion of strong ion gaps (SIG). SIG may be estimated (eSIG) based on unmeasured ions, similarly to the classic notion of anion gap.[12]

- $eSIG = anion\ gap - [A^-]$

SIG is usually close to zero. MAC with increased SIG is caused by unmeasured anions, whereas MAC with SIG ~ 0 usually is caused by chloride retention (Table 2). Assessment of SIG seems useful to detect unmeasured anions in critically ill patients, hypoalbuminemic patients with normal pH, base excess and anion gap.[12]

Making a parallel between the analysis of ABD using the classical approach and that proposed by Stewart, it is possible to conclude that the rational use of alkali therapy with sodium bicarbonate would be adequate in most cases of MAC with reduced SID and SIG (Table 2). It is interesting to note that, according to Stewart's physicochemical principles, it is the sodium contained in the sodium bicarbonate infusion that causes the increase in serum bicarbonate, since serum bicarbonate, being a dependent variable, would not be capable of acting directly on the acid-base balance. The supply of sodium would thus increase SID: $[Na^+ + K^+ + Mg^{++} + Ca^{++}] - [Cl^- + lactate^-]$. Another factor that may contribute to the increase in SID is the decrease in chloride secondary to the dilution effect induced by the administration of sodium bicarbonate, which does not contain chloride.[3]

Although the Stewart approach is based on sound physicochemical and mathematical principles, in clinical practice the traditional analysis of ABD, taking into consideration blood gases, anion gap and the knowledge concerning mechanisms of metabolic and electrolytic compensation is still current after decades of being established. In addition, it provides a didactic and rational view in normal and pathologic situations. Other important aspects concerning Stewart's theory would be the complexity of the physicochemical and mathematical equations and the need for computed analysis of the effects of the three independent variables, with possible loss of accuracy and involving the calculation of small differences.

Table 2 - Classification of metabolic disturbances based on Stewart's physicochemical model

Metabolic acidosis	
Low SID; high SIG	Ketoacids, lactic acid, salicylates, formaldehyde, methanol
Low SID low SIG	Renal tubular acidosis, total parenteral nutrition, anion exchanging resins, diarrhea, pancreatic losses
Metabolic alkalosis	
Low serum albumin	Nephrotic syndrome, liver cirrhosis
High SID	
Chloride loss	Vomiting, loss of nasogastric tube, diuretics, posthypercapnia, villous adenoma, mineralocorticoid excess, hyperaldosteronism, Cushing's syndrome, exogenous corticosteroids, licorice
Sodium overcharge (acetate, citrate, lactate)	Ringer lactate solution, total parenteral nutrition, blood transfusion
Other	Severe intracellular cation deficiency: K^+, Mg^{++}

Source: Adapted from Corey[12] and Kellum.[16]
SID = strong ion difference; SIG = strong ion gap.

Effects of acidemia

The effects of acidemia on the organism are fairly known, with special emphasis on cardiovascular complications, and depend on the underlying disorder and the intensity and speed of presentation.[10]

Classically, severe acidemia (pH < 7.1), through its action on enzyme function and protein metabolism, inhibits myocardial contractility, predisposes to severe arrhythmias, reduces peripheral vascular resistance, decreases hemoglobin oxygen affinity and causes arterial vasodilation and venous vasoconstriction, resulting in hypoperfusion of organs such as liver and kidney, among many other metabolic, electrolytic and hormonal effects.[6,7] These complications are responsible for the mortality associated with acidemia.[2]

Nevertheless, these effects are heterogeneous and depend on the type, magnitude and experimental model. Thus, myocardial contractility is reduced in animal isolated heart preparations, but the picture is complicated when aspects such as interaction and activation of sympathetic and adrenal systems during acidosis are considered. The responsiveness of adrenergic receptors is usually decreased in the presence of circulating catecholamines.[17,18]

One point to be considered is the potential protective effect of extracellular acidosis in anoxic cells. The metabolic activity of isolated neurons and heart cells correlates with medium pH, with reduced synthesis in situations of acidosis.[19-22] On the other hand, hypocapnic alkalosis may worsen lung cellular lesion in experimental ischemia models.[23] Thus, acidemia would temporarily provide protection to anoxic cells with reduced metabolism. This fact raises a question and provides an argument against the need to decrease $[H^+]$ in critical situations.[3,4]

Adverse effects of sodium bicarbonate use

Regardless of any possible or unlikely benefits, the use of sodium bicarbonate has many undesirable effects on the organism, such as deterioration of hemodynamic status associated with volume overload, hyperosmolarity, paradoxical cerebrospinal fluid acidosis, increase in the production of organic acids and reduction of intracellular pH.[2,24,25]

Sodium bicarbonate contains a large amount of CO_2 (50 mEq ~ 260-280 mmHg). In plasma, CO_2 is released and diffused into cells faster than bicarbonate, causing a paradoxical increase of pCO_2 and decrease of intracellular pH, which may cause paradoxical cerebrospinal fluid acidosis and neurological complications. Other dangerous side effects include: superimposed alkalemia, hyperosmolarity, hypernatremia, hypocalcemia, hypokalemia, risk of brain hemorrhage in neonates, deviation to the left in the oxyhemoglobin dissociation curve (reducing the supply of tissue O_2), etc.[2,3,6,10]

However, some authors question the relevance of experimental studies and the referred morbidity and mortality, arguing for the use of alkali therapy in severe situations.[26]

Lactic acidosis

Serum lactate is considered a mortality marker in critically ill patients. Lactic acidosis is basically caused by hyperproduction or underutilization of lactic acid.[13,25,27,28] In the first situation, the organism needs to regenerate ATP under tissue hypoxia, whereas in the second case there are disturbances in the removal of lactic acid through oxidation or glucose conversion mechanisms.[25,28] The main situations observed in pediatric intensive care are sepsis, severe hypoxemia, cardiogenic shock, liver failure and intoxication. In sepsis, other mechanisms, in addition to tissue hypoxia, are probably involved in the generation of lactic acid, probably related to changes in intermediate metabolism.[25,29]

Heterogeneous studies, both experimental and clinical, using sodium bicarbonate in LA, have shown reduced cardiac output, intracellular acidemia, reduced liver flow and increased serum lactate.[30-32] In addition to these hemodynamic alterations, an increase in venous pCO_2 was also observed along with reduction in liver and myocardial pH. Nevertheless, using an experimental rat model of LA, Halperin observed longer survival in animals receiving hypertonic sodium bicarbonate.[33]

Studies with adult humans have reported limited effects of sodium bicarbonate on LA. These studies have not observed increased survival or significant hemodynamic improvement with or without increase in serum pH.[34-36]

Although no benefits of sodium bicarbonate have been demonstrated in usual doses, administration of high doses associated with hemofiltration in patients with septic shock and LA reduced overall mortality.[37] Conversely, the use of sodium bicarbonate in patients with severe cardiovascular disease was harmful.[38]

A literature review published in 2004, evaluating ancillary therapies in sepsis, established that the use of SB is not recommended for hemodynamic improvement or reduction in vasopressors in LA with pH > 7.15 (class C recommendation), with uncertain indication for pH < 7.15 (class E).[39,40]

In summary, most adult patients with LA treated with conventional doses of SB do not experience hemodynamic improvement or reduced morbimortality.[2,41] These results must also take into account the side effects related to the use of SB (intracellular acidosis, hyperosmolarity, hypocalcemia,

hypervolemia, etc.). Other therapies, such as tromethamine (THAM), dichloroacetate and hemofiltration will be discussed in detail below.

Most authors agree that the most effective treatment for LA is the adequate and timely treatment of the underlying disease, improvement of tissue oxygenation, restoring of volemia, use of vasoactive drugs, modulation of septic status (control of infection and rational strategy with antimicrobial therapy) and improvement of myocardial function.[28,41,42] There are promising potential agents applied in isolation or in association, such as dichloroacetate and dialysis methods. In any case, randomized controlled studies focused on pediatric populations are still lacking.

Diabetic ketoacidosis

In MAC, severity is associated with high morbidity, especially due to central nervous system complications such as brain edema. The primary event in the pathophysiology of DKA is insulin deficiency resulting from failure of pancreatic cells associated with counter-regulatory mechanisms, such as stress, sepsis and hormones (that is, glucagon, catecholamines, cortisol and growth hormone).[10,43] All these factors contribute to stimulate glycogenolysis and gluconeogenesis and to reduce the use of glucose, causing marked hyperglycemia, osmotic diuresis, loss of electrolytes, dehydration and decreased glomerular filtration rate (GFR). At the same time, there is an increase in lipolysis with generation of the ketoacids acetoacetate and β-hydroxybutyrate, which cause MAC by overloading the organism's buffer capacity. This acidosis is further worsened by LA resulting from decreased tissue perfusion.[9,10,43] All these associated factors contribute to increase the level of stress, causing the organism to release an even higher amount of counter-regulating hormones, establishing a vicious circle of metabolic decompensation and increased acidosis.

The production of ketoacids in DKA determines an increase in anion levels and in the serum anion gap. However, it is speculated that there could be an initial failure in the reabsorption of β-hydroxybutyrate, and that these anions would probably be excreted through urine in the form of sodium or potassium salts instead of ammonium salts. This would result in indirect loss of bicarbonate, a loss that would not be immediately detected due to the contraction of extracellular space following osmotic diuresis and dehydration. This β-hydroxybutyrate excretion would lower the increase in serum anion gap as well as the excretion of ammonium, with indirect loss of bicarbonate, in theory leading to the need to later restore exogenous bicarbonate levels. In addition, the contraction of extracellular space would result in decreased renal and brain metabolism of β-hydroxybutyrate, with sudden increase in the severity of DKA, which could result in the need to replenish bicarbonate at this stage.[44]

The primary approach to DKA consists of volemic and hydroelectrolytic replacement, with special attention to potassium, and also of insulin therapy. The permanent MAC in this condition is reversed through this approach, by interrupting the cycle of ketoacid formation with administration of insulin, increasing the removal of these acids with adequate volemic replacement and subsequent improvement of GFR and minimization of LA through improved tissue perfusion.

The discussion concerning the use of bicarbonate in DKA has long been a controversial matter, with pros and cons. Many clinical studies have shown that the use of bicarbonate had no beneficial effects as compared to the aforementioned conventional approach.[45-48] Besides, bicarbonate has been blamed for undesirable metabolic effects, such as delayed regulation of lactate balance,[49] decrease in the recovery of ketone body metabolism with increase in liver ketogenesis[50] and increased risk of brain edema in children.[51] These studies, carried out in adults, did not recommend sodium bicarbonate therapy in DKA associated with pH > 7.0. They also conclude that additional randomized and prospective clinical studies are necessary to determine the efficacy of alkalis for DKA treatment (especially with pH < 6.9).

The current recommendation concerning the use of sodium bicarbonate in children and adolescents by the American Diabetes Association is limited to selected patients, including those with severe acidemia (pH < 6.9), in whom the decreased myocardial contractility and the peripheral vasodilatation caused by acidemia would worsen tissue perfusion, and in patients with severe hyperkalemia.[43] The European Society for Paediatric Endocrinology also suggests that alkalis should also be employed in the selected cases described above.[52] This discussion continues to generate debate in the scientific literature,[53-56] and the controversy has been fueled by a deeper examination of the physiological events in this disorder.

Cardiopulmonary resuscitation

For a long time, sodium bicarbonate was an essential drug in the treatment of acidosis secondary to cardiorespiratory arrest (CA). However, the increased knowledge concerning pathophysiological mechanisms has considerably changed the vision of treatment. Currently, the routine use of sodium bicarbonate is no longer recommended.[57] Post-CA acidemia results from an increase in tissue CO_2 due to the associated ventilatory failure and the LA resulting from anaerobic metabolism and hypoxemia.[2,3] Acidemia would increase with the administration of sodium bicarbonate, promoting intracellular acidosis.[57,58] However, in an experimental study

in which animals had their myocardial perfusion maintained with the use of adrenalin and were submitted to hyperventilation, thus removing the accumulated CO_2, the use of sodium bicarbonate was beneficial, increasing the post-CA resuscitation rate.[59] Increased survival was also shown in dogs submitted to prolonged CA receiving sodium bicarbonate when compared to a control group.[60] Bar-Joseph, in a recent retrospective analysis of a collaborative prospective multicenter study has reported benefits with early use of sodium bicarbonate in adults with out-of-hospital CA, showing more favorable cardiopulmonary resuscitation and neurological outcomes after long-term follow-up.[61] In 2006, Vukmir analyzed adults with CA in a pre-hospital environment, and was unable to detect any differences in survival between those receiving or not sodium bicarbonate. However, survival was increased in patients with prolonged CA (> 15 min) who received sodium bicarbonate, compared to those who did not receive it. This leads to a discussion concerning the possibility that the use of sodium bicarbonate may be beneficial in prolonged cardiopulmonary resuscitation.[62]

The American Heart Association (AHA) does not recognize benefits from the use of sodium bicarbonate in CA (undetermined level of evidence). The AHA accepts the use of sodium bicarbonate in the presence of non-responsive CA after ventilation and chest maneuvers combined with adrenalin and volemic replacement in the following situations: severe MAC despite effective ventilatory support, hyperkalemia, hypermagnesemia, intoxication with tricyclic antidepressants and calcium channel blockers and prolonged CA (class IIb).[57]

Systematic reviews have not provided evidence of benefits from the administration of sodium bicarbonate for the reduction of CA mortality and morbidity in neonates in the delivery room or in premature newborns with MAC.[63-65]

Sodium bicarbonate treatment and replacement

Despite the controversy surrounding the use of SB, we generally use intravenous bicarbonate, especially in situations of MAC with normal anion gap, in the presence of serum pH < 7.10 and/or plasma bicarbonate < 10 mEq/L, under adequate hemodynamic conditions, hydration and ventilation. Special treatment considerations must be made in DKA, presentations with lung involvement, renal tubular acidosis, acute and chronic renal failure, CA, neonatal period, specific situations of intoxication, inborn errors of metabolism, associated electrolytic disorders (hypokalemia, hypocalcemia), among others. Bicarbonate deficit may be estimated taking into account the base excess or excess pCO_2 derivative on gasometry. Base excess is a calculated value, derived from partial CO_2 pressure and arterial pH, assuming normal water, electrolyte and albumin contents, which makes the interpretation of this parameter more prone to error.[66] In equilibrium situations, it is estimated that the desired bicarbonate level should be close to 0.5-0.6 of pCO_2, or else a desired level close to 15 could be adopted; this is a relatively safe value, since the respiratory compensation to be promoted will result in pCO_2 close to 30 mmHg. The distribution volume of bicarbonate is equivalent to the extracellular fluid volume, that is, 60 or 70% (small children) of the body weight. However, the adoption of 30% is usually sufficient for recovery from a critical situation and to avoid risks and potential side effects.[42]

1) HCO_3^- (mEq) deficit = $[HCO_3^-{}_{desired} - HCO_3^-{}_{actual}]$ x weight (kg) x 0.3

   where $HCO_3^-{}_{desired}$ = 15 mEq.

2) HCO_3^- (mEq) = BE (mEq/L) x 0.3 x weight (kg)

   where BE = base excess.

The intravenous bicarbonate solution should be as isosmolar as possible (about 1.5%), with the necessary dilutions depending on the presentation (3, 8.4 or 10%, containing 0.36, 1 and 1.2 mEq/L, respectively). Ideally, it should be administered through a central venous line or diluted with distillated water. Depending on the severity, we use half the calculated dose, administered between 1 and 4 hours; after that, a new gas measurement and clinical assessment become necessary. The initial objective is to maintain pH slightly above 7.20, recovering the patient from a situation of severe acidemia. The infused volume and amount of sodium provided simultaneously must be considered. If there is acute renal failure or hyperosmolarity, as in situations of hypernatremia, the possibility of dialysis should be considered.

Other treatment alternatives

As the adverse effects of sodium bicarbonate are described and its use in clinical practice is challenged, clinical studies focused on the treatment of MAC have introduced alternative therapies.[67] Noteworthy among these therapies are Carbicarb, tromethamine, dichloroacetate, thiamin and pyruvate. We will also discuss the role of renal replacement therapy in the management of MAC.

Carbicarb

Carbicarb is an equimolar mixture of sodium bicarbonate and sodium carbonate. This drug has a superior alkalinizing effect as compared to sodium bicarbonate, allowing a reduction of tissue CO_2 generation.[4,42] It is suggested that the clinical use of Carbicarb is advantageous in situations of MAC with high anion gap, since the disorder would be established through an increase in CO_2 generation. However, Carbicarb is more consistent than sodium bicarbonate in decreasing intracellular pH. Its final hemodynamic effects have not yet been established.[4,68] Used at low doses during

CA, Carbicarb is thought to attenuate brain acidosis, increasing the success of resuscitation procedures and decreasing neurological deficit and neuronal death in the hippocampus. However, at high doses it may increase neurological damage and neuronal death after post-asphyxia CPR; in addition there is risk of hypervolemia and hypertonicity similar to that associated with bicarbonate.[42,69] Carbicarb is not available for clinical use, and additional studies are required to evaluate its efficacy and benefits.

Tromethamine

Tris (hydroxymethyl) aminomethane (THAM) is a weak amino alcohol base with more buffer power than sodium bicarbonate (pK = 7.82 *versus* 6.1, respectively). It is efficacious in both metabolic and respiratory acidoses. It is excreted by kidneys and does not increase the production of CO_2, thus decreasing the need to adjust ventilation in patients under treatment.[70] Its easy cellular diffusion translates into potential to increase intracellular pH.[71] The isolated use of THAM has been shown to increase myocardial inotropism, however the substance was not efficacious to buffer arterial pH. However, in combination with sodium bicarbonate, it reduced myocardial depression, improved hypercapnia and corrected acidosis in experimental studies.[70,71] On the other hand, adverse side effects have been described, such as hypoglycemia, hyperkalemia, local necrosis by extravasation during peripheral intravenous administration and liver necrosis in neonates.[72]

Dichloroacetate

Dichloroacetate (DCA) is a chemical substance produced by water chlorination and metabolism of substances used in chemical industries. It is of great toxicological interest.[7,10] The clinical application of DCA in LA has been studied due its pharmacodynamics.[73,74] Since LA may be associated, at least in part, with a deficiency in pyruvate oxidation, the use of DCA, stimulating pyruvate dehydrogenase, promotes oxidation of pyruvate in acetyl-coenzyme A, reducing the production of lactate. Although the use of DCA has produced beneficial effects on arterial pH and lactate levels, especially in children with congenital LA, there has not been an impact in the associated mortality or improvement of hemodynamic conditions. In addition, its toxic effects have not been adequately established, requiring further studies.[73] Recently, there has been growing interest in DCA, mainly to treat inborn errors of metabolism and mitochondrial diseases, with evidence of benefits in these cases.[74,75]

Thiamine

Thiamine is an essential cofactor of pyruvate dehydrogenase. Exogenous administration of thiamine is indicated in the presence of thiamine-deficiency (beriberi) related acidosis and extended to patients as risk, such as in chronic alcoholism, neoplasias, short bowel syndrome and HIV carriers using nucleoside reverse transcriptase inhibitors. Nevertheless, its efficacy in LA has not been established by clinical studies.[4]

Pyruvate

The interest in using sodium pyruvate stems from its protective effect for vital organs, especially against myocardial ischemia and post-reperfusion lesions, in addition to its buffer effect in many clinical situations. Pyruvate is thought to be more effective than other buffers in the treatment of severe acidemias; not only does it correct arterial pH, but also intracellular pH, and improves underlying cellular lesions in critical patients with multiple organ and system dysfunctions. As with any other drug, a final conclusion depends of further clinical studies to establish its efficacy and adverse effects.[76]

Renal replacement therapy

The use of dialysis therapies, such as hemodialysis (HD) and continuous venovenous hemofiltration and hemodiafiltration, has been shown to be useful to treat ABD associated with acute renal failure.[5] In general, continuous dialysis therapies are more advantageous than intermittent therapies to correct MAC, with a faster and longer lasting effect.[77] Once the mechanisms that generate MAC in acute renal failure have been established (increase in unmeasured anions, hyperphosphatemia and hyperlactatemia), the changes in acid-base balance after continuous dialysis therapies are introduced can be explained by the decrease in SIG and chloride and phosphate concentrations. During hemofiltration, there is loss of endogenous bicarbonate, which is constantly replaced with an alkali (lactate, acetate, citrate or bicarbonate), producing a buffer effect and increasing plasma pH. The effects on acid-base balance depend on the dose used and on the metabolic activity, and may correct severe acidosis.[78-80] Isolated reports have shown the efficacy of this method.[81] More recently, good results have been obtained with high-volume hemofiltration, especially concerning the hemodynamic status of patients in septic shock.[82] However, a review of evidence-based literature has not shown advantages of hemofiltration as compared with intermittent hemodialysis as ancillary therapy in sepsis and acute renal failure.[39,40]

Peritoneal dialysis has been used in patients with contraindication for hemodialysis, especially those with severe hemodynamic instability, and also because it is easy to use and its use has become traditional in pediatrics. Although it is not the therapy of choice to treat MAC, the use of solutions containing sodium bicarbonate is beneficial to the acid-base balance, with greater efficacy if compared to lactate solutions in children.[83,84]

Currently, additional controlled studies are required to establish criteria and evidence of the benefits of using these continuous renal therapy methods in severe MAC, especially in LA.

Conclusions

New findings and studies currently guide treatment in many situations that have long been known and met in daily practice. MAC is one of them. There is consensus regarding alkali and sodium bicarbonate replacement in cases of normal anion gap acidosis involving primary loss of bicarbonate. However, treatment with sodium bicarbonate, extensively used in the past, is being abandoned or used with restrictions in CA, LA and DKA; since there is no evidence of benefits, routine use is no longer indicated. The current trend is to question its use in several situations associated with high anion gap acidemia, because of the many adverse effects observed and of the potential protective effect of acidemia in these critical situations. Despite the controversy, there is agreement regarding the mechanisms causing metabolic acidemia and the need to treat the underlying disease and as early as possible.

However, taking into consideration the anxiety caused by the challenge of facing severe acidemia, with its life-threatening complications, and the difficulty of changing paradigms, new, more specific, studies are called for to propose an evidence-based rationale for the use of sodium bicarbonate. A diagnostic strategy based on pathophysiological knowledge of ABD and prompt treatment to reverse the primary mechanisms causing MAC in each patient will lead to a more rational use of sodium bicarbonate therapy. Other therapies require larger and better clinical trials in both adults and children, with emphasis on alternative MAC treatments with fewer side effects.

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