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INDICATIONS FOR USE OF BICARBONATE IN PATIENTS WITH METABOLIC ACIDOSIS

A. I. ARIEFF

Identifying the indications for use of bicarbonate in patients with metabolic acidosis has led to a major controversy in the fields of intensive therapy, medicine and anaesthesia, with numerous editorials expressing disparate opinions over the past 4 years [9, 33, 64, 94]. There have been substantial disagreements between various groups over the indications, or lack of them, for the use of bicarbonate. This article reviews the rationale for use of sodium bicarbonate in the management of patients with metabolic acidosis.

CLASSIFICATION OF METABOLIC ACIDOSIS

Metabolic acidosis can be broadly defined as a condition characterized by an arterial pH less than 7.35 and a bicarbonate concentration less than 21 mmol litre^{-1} in the absence of arterial hypercapnia. These biochemical findings imply addition to the extracellular fluid of an acid load, which may be either exogenous or endogenous. When the body is presented with an acid load, there is titration by various fixed buffers, both intracellular and extracellular. The intracellular buffers consist primarily of proteins and polypeptides, while extracellular buffers include haemoglobin, plasma proteins and creatinine. In general, because of the buffering capacity of the body, there will be no change in the plasma concentration of bicarbonate until all fixed buffers have been exhausted. Thus, when patients with metabolic acidosis demonstrate a measurable decrease in plasma concentration of bicarbonate, the indication is that all other available intra- and extracellular buffers have been exhausted.

There are several varieties of metabolic acidosis, and one method of classification is on the basis of the "anion gap" [65]. The anion gap (AG) is defined as the molar concentration of sodium ($[Na^+]$) in blood minus those of chloride ($[Cl]$) and bicarbonate ($[HCO_3^-]$) [34, 68]:

$$AG = [Na^+] - ([Cl^-] + [HCO_3^-]) \qquad (1)$$

(normal range 9–14 mmol litre^{-1}). Thus metabolic acidosis may be classified according to whether the anion gap is normal, decreased or increased. Increased anion gap metabolic acidosis includes those disorders of acid–base metabolism in which there is acidosis because of the presence of increased quantities of organic acid(s). Such organic acids may be either endogenous (keto-acids, lactic acid) or exogenous (salicylate, paraldehyde). Those forms of metabolic acidosis with normal or decreased anion gap are primarily the renal tubular acidoses.

It has been proposed that metabolic acidosis with increased anion gap can be further classified into those clinical conditions in which tissue hypoxia is either present or absent [3] (table I). Tissue hypoxia is present theoretically in all forms of lactic acidosis in general, the acidosis of cardiac arrest in particular, and in a substantial number of patients who are critically ill, even if the blood concentration of lactate is not increased [13]. This is because depressed total body oxygen utilization will not result in increased lactate production until a critically low rate of oxygen use is reached. At this critical value, arterial lactate concentration may increase quite rapidly, often giving the impression that there is an acute

KEY WORDS

Acid–base equilibrium: metabolic acidosis, bicarbonate, buffers. Hypoxia. Complications: arrest.

ALLEN I. ARIEFF, M.D., F.A.C.P., Divisions of Geriatrics and Nephrology, Department of Medicine, Veterans Affairs Medical Center and University of California School of Medicine, San Francisco, California, U.S.A.

Address for correspondence: Department of Medicine, V.A. Medical Center (111G), 4150 Clement Street, San Francisco, CA 94121, U.S.A.

TABLE I. *Metabolic acidosis with and without tissue hypoxia*

With hypoxia	Without hypoxia
Cardiac arrest	Uraemic acidosis
Lactic acidosis	Renal tubular acidosis
Pulmonary oedema	Diarrhoeal illness
Gram negative sepsis	Exogenous intoxications
	Salicylate
	Methanol

disturbance of tissue oxygenation whereas, in fact, there has been depressed use of oxygen for some time [5, 13, 31]. Tissue hypoxia is, generally, not present initially in most other forms of metabolic acidosis, in particular diabetic ketoacidosis, uraemic acidosis, most exogenous intoxicants (ethylene glycol, paraldehyde, methanol), renal tubular acidosis and the acidosis of diarrhoeal disease [33]. It is particularly important to distinguish those metabolic acidoses which are associated with tissue hypoxia, because it appears that therapy of such disorders, which often includes administration of sodium bicarbonate ($NaHCO_3$), frequently makes the acidosis worse [25, 39, 99]. However, administration of sodium bicarbonate to patients who have metabolic acidosis which is not associated with tissue hypoxia is often beneficial [33].

OXYGEN AND HYPOXIC METABOLIC ACIDOSIS

Hypoxia and source of hydrogen ions

In most instances where there is metabolic acidosis in the presence of tissue hypoxia, the predominant extracellular acid anion will be lactate. Lactic acid is formed primarily by anaerobic glycolysis because of a deficiency of available oxygen. It must be borne in mind that the extracellular abnormalities associated with metabolic acidosis have no necessary relationship to the intracellular changes. In particular, the effects of hypoxia on the heart are substantially different from those in other tissues [40, 78, 100]. Contrary to common perceptions, most of the intracellular H^+ ion in patients suffering cardiac arrest comes not from lactic acid but from "metabolic" carbon dioxide [78] and H^+ ion from the hydrolysis of ATP [48, 105] (table II). In hypoxic states, there is increased anaerobic metabolism, with increased generation of metabolic carbon dioxide and decreased generation of ATP. A major mechanism for removal of H^+ ion from myocardial cells is via the Na^+–H^+ antiporter, with transport of H^+ out of cells in exchange for Na^+ ion [42]. Sodium is then transported back out of cells via the Na^+–K^+ ATPase system. This system is energy dependent. In the presence of hypoxia, less ATP is available, leading to progressive intracellular acidosis as a result of accumulation of metabolic carbon dioxide and H^+ ion.

TABLE II. *Sources of hydrogen ion in hypoxic metabolic acidosis*

Tissue H^+ ion	Blood H^+ ion
Hydrolysis of ATP	Lactic acid
Metabolic carbon dioxide	Other
Lactic acid	Short chain fatty acids
	Renal failure

Hypoxia and the cardiovascular system

In the development of lactic acidosis associated with tissue hypoxia, the critical factors are the performance of the heart and lungs, and the subsequent delivery of oxygen to the tissues. Because of this, it is important to review the regulation of systemic and myocardial oxygen delivery and utilization. The critical role of the heart in the development of lactic acidosis is often not appreciated [3, 4]. Similarly, total body oxygen utilization may be substantially impaired without a measurable increase in arterial lactate concentration [13, 31]. Finally, measurements of arterial blood-gas tensions and lactate concentrations are often of no use in determining the acid–base and oxygenation status of either the "whole body" or the heart [1, 13, 58, 78, 100].

Metabolic acidosis: hypoxic and normoxic

If one attempts to predict the response to therapy in patients with metabolic acidosis, it appears that a more useful classification of metabolic acidosis would be based on whether the condition is or is not associated with tissue hypoxia (table I). In general, when there is metabolic acidosis in the presence of tissue hypoxia, available tissue oxygen is not adequate for the individual's metabolic needs. Treatment of the metabolic acidosis with sodium bicarbonate tends to limit further the available oxygen and thus lead to increased production of lactate, actually worsening the metabolic acidosis (table III). However, if the metabolic acidosis is not

TABLE III. *Treatment of metabolic acidosis with sodium bicarbonate*

With hypoxia	Without hypoxia
Increase in blood P_{CO_2}	No change in oxygen utilization
Decrease in blood pH	No change in lactate production
Decrease in tissue O_2 delivery	Increase in arterial pH
Decrease in coronary blood flow	

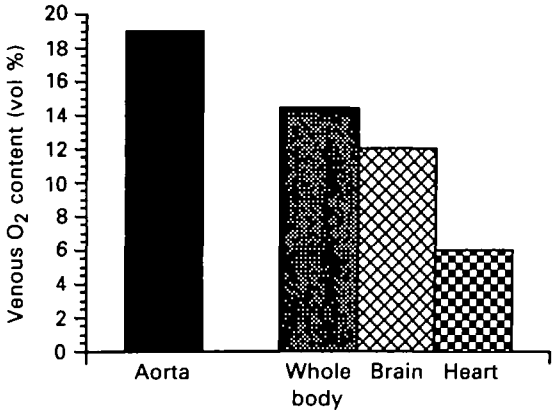

FIG. 1. Oxygen content in aorta and venous blood in normal humans. The oxygen extraction reserve may be calculated as the venous oxygen content as, in severe hypoxia, all available oxygen may theoretically, be extracted. It is apparent that the oxygen reserve of either "whole body" or brain is at least twice that of the heart. Thus in hypoxic states the heart has less oxygen reserve than any other organ or tissue in the body.

associated with tissue hypoxia (renal tubular acidosis, diarrhoeal illness, uraemic acidosis), bicarbonate may increase the arterial pH and prove beneficial [37, 76, 83] (table III).

In animals with hypoxic lactic acidosis, even with a mean arterial P_{O_2} as small as 4 kPa, the total body oxygen consumption appears not to change [5, 56]. This occurs largely because of the combined effects of increases in both cardiac output and oxygen extraction by the body. This combination has the effect that the actual amount of oxygen used does not change significantly (assuming the heart is capable of increasing its output). However, the distribution of oxygen use is not uniform. Oxygen utilization by gut, liver, kidney and muscle all decline. The result is an increase in production of lactate by gut and muscle, while extraction of lactate by liver decreases. Oxygen use by brain and heart almost certainly increases in the presence of tissue hypoxia. Thus hypoxic lactic acidosis is partly a result of a redistribution of available oxygen such that utilization by heart and brain are preserved, while that by gut, liver, kidney and skeletal muscle is not. These changes depend on the ability of the heart to increase cardiac output in response to a decreased arterial P_{O_2}. If this response does not occur, the animal (or patient) will not survive. In patients with heart disease, the ability of the individual to increase cardiac output in response to a hypoxic situation is limited by the amount of reserve cardiac function, as well as the oxygen reserve described previously [12, 13, 18, 104] (fig. 1).

Another reason for the development of lactic acidosis relates to a decrease in hepatic lactate extraction. In hypoxia, this is probably related to both a decreased liver uptake of oxygen and a decrease in hepatic intracellular pH (pH_i) [73]. In summary, then, the pathogenesis of experimental hypoxic lactic acidosis is multifactorial. There is increased lactic acid production from both gut and skeletal muscle. The increase in production of lactate corresponds with a reduction of oxygen utilization by gut and skeletal muscle. Cardiac output, despite the presence of metabolic acidosis, is initially increased. Although it is commonly accepted that acidosis decreases cardiac output, in reality this is related to the pH_i of the heart, not the extracellular pH [39, 67, 95, 97]. In fact, survival of patients with cardiac dysfunction correlates best with myocardial ischaemia and intracellular acidosis [51]. The liver is unable to increase its lactate extraction to that which it ordinarily can achieve, and is associated with a highly significant decrease in hepatic pH_i, which is known to inhibit the ability of the liver to extract lactate. Lastly, impaired cardiac output, ischaemia (decreased organ blood flow) and extracellular metabolic acidosis do not appear to be important in the pathogenesis of hypoxic lactic acidosis.

BLOOD-GASES: ARTERIAL *VS* MIXED VENOUS

It is now clear from studies in both laboratory animals [6, 37, 58] and human subjects [1, 13, 100] that arterial blood-gas tensions are at best a poor indication of the acid–base and tissue oxygenation status of the body. Measurement of

arterial blood-gas tensions evaluates the performance of the lungs, and the lungs can affect only the blood which has just passed through them. In low-flow states with impaired venous return, cardiac output, or both, arterial blood may be relatively normal while mixed venous blood demonstrates severe acidosis, hypoxia, or both [1, 100]. Measurements must be made of the arterial and mixed venous (pulmonary artery) gases, including oxygen content (which can be determined from the oxygen saturation and haemoglobin). As a practical matter, central venous gases are similar enough to mixed venous (pulmonary artery) gases that they can be used when a pulmonary artery catheter cannot be placed in the patient [1]. Oxygen transport (or delivery) may be calculated using the product of the arterial oxygen content and blood flow (usually expressed as oxygen ml min^{-1}). It represents the quantity of oxygen available or delivered to the whole body or to individual organs or tissues, and is maintained preferentially to the "vital organs" during hypoxia by a number of adaptive mechanisms [18, 43, 87]. The ability of tissues to increase oxygen extraction when oxygen delivery is inadequate is termed the oxygen extraction reserve or the oxygen utilization coefficient [20, 41, 88]. Because, in hypoxic states, tissues are theoretically capable of extracting virtually all of the oxygen carried to them by haemoglobin, the oxygen extraction reserve represents the amount of oxygen which is not extracted by tissues and, theoretically, is available [60]. Under normal aerobic conditions, this oxygen extraction reserve is quite large (fig. 1). However, because resting requirements for oxygen are greater per gram of tissue in the heart than in any other organ, resting oxygen extraction will be much greater there: about 60–65%. Consequently, the heart has the smallest extraction reserve, and can only increase resting oxygen extraction by a maximum of about 50%. This is in marked contrast to the body as a whole, which has an oxygen reserve which is three times the normal resting oxygen extraction (fig. 1). With profound hypoxia, circulatory adjustments become increasingly important to maintain adequate oxygen delivery to the heart and brain. There is a generalized reduction of oxygen utilization in most of the "non-vital" organs, such as skeletal muscle, liver and gastrointestinal tract, with preferential utilization by heart and brain. The failure of such adjustments leads to intracellular acidosis and eventual organ failure.

SODIUM BICARBONATE AND METABOLIC ACIDOSIS

General considerations

Sodium bicarbonate has been used in the treatment of metabolic acidosis for more than 50 years and has almost become a matter of routine. This practice was continued without any serious question of its metabolic and systemic actions until about 1980. The rationale has been the implied logic of administering a base to correct an acidotic state. Theoretically, sodium bicarbonate should react with the hydrogen ion from an organic acid:

$$HAc + NaHCO_3 \rightarrow NaAc + H_2O + CO_2 \quad (2)$$

where Ac represents the (an)ion of an organic acid.

The above reaction should remove the H^+ ion by its chemical conversion to water, with removal of the carbon dioxide via the lungs. In fact, in patients with renal tubular acidosis, diarrhoea and uraemic acidosis, the arterial pH frequently improves with the administration of sodium bicarbonate. Such patients generally do not have problems of tissue oxygenation, and in these situations bicarbonate often appears to be of benefit. However, administration of sodium bicarbonate has several disadvantages, including: venous hypercapnia with an increase in mixed venous carbon dioxide content [14, 44], leading to a decrease in tissue pH_i [6, 37, 86]; a decrease in the pH of cerebrospinal fluid [76, 79]; tissue hypoxia [12, 16, 55]; circulatory congestion [89]; hypernatraemia [59, 89]; hyperosmolality with brain damage [89, 90]. Whereas sodium bicarbonate is often of benefit in patients with metabolic acidosis in the absence of tissue hypoxia, some patients with diabetic ketoacidosis or hepatic failure will have impaired tissue oxygen delivery and the aforementioned complications of sodium bicarbonate are likely to develop. Additionally, in most patients with cardiac arrest, shock or sepsis, impaired tissue oxygen delivery is the primary cause of lactic acid accumulation. In these situations, the administration of sodium bicarbonate does not appear to affect the underlying tissue hypoxia and is generally not successful in improving either acidotic state or clinical status. Thus the underlying cause of lactic acid accumulation appears to dictate if the administration of sodium bicarbonate will be of benefit (table III).

In an early study of patients with lactic acidosis [99] given large amounts of i.v. bicarbonate, there was essentially no change in either arterial pH or the clinical condition of these patients. None survived. In patients with cardiac arrest, sodium bicarbonate increases the mixed venous and arterial P_{CO_2} [14, 59, 100] without either decreasing the blood concentration of lactate or increasing that of bicarbonate. The result is either no change or a net reduction of the blood pH when compared with observations if sodium bicarbonate is not used. Moreover, the administration of large amounts of bicarbonate (mean 180 mmol litre^{-1}) during cardiac arrest [59] resulted in severe hypernatraemia, hyperosmolality, increasing lactic acidosis and no survival. These observations and others have apparently led to continuing recommendations by the American Heart Association that the amount of bicarbonate administered to patients suffering cardiac arrest should be reduced. Current guides for the management of cardiopulmonary arrest no longer recommend the routine use of sodium bicarbonate [66].

Hypercapnia

The arterial P_{CO_2} is determined by the ratio of production of carbon dioxide to alveolar ventilation; it is directly proportional to production of carbon dioxide and inversely proportional to alveolar ventilation [101]. Thus increased generation of carbon dioxide by administration of bicarbonate will actually increase the venous P_{CO_2} if there is impaired cardiac output (because of decreased delivery of venous carbon dioxide to the lungs) or a decrease in alveolar ventilation. Carbon dioxide readily diffuses into cells such that the intracellular P_{CO_2} approaches that of mixed venous blood. In a closed system, carbon dioxide accumulates after administration of bicarbonate, thereby decreasing the pH [71]. The effects of decreased alveolar ventilation may be imitated by addition of sodium bicarbonate to a closed system *in vitro*. In an *in vitro* system, sodium bicarbonate did not normalize the pH of acidified blood [52]. These results and others utilizing sodium bicarbonate in an acidotic *in vitro* system demonstrate that it does not increase the pH of blood when there are constraints to the removal of carbon dioxide from the system [71]. Such a situation may occur clinically in states characterized by low pulmonary blood flow, such as heart failure, shock, cardiac arrest and haemorrhage. Numerous *in vivo* studies demonstrate that administration of i.v. bicarbonate to humans with either metabolic acidosis or heart failure results in an increase in blood P_{CO_2} [12, 25, 26, 57, 59, 78, 100, 102]. In laboratory animals with various forms of metabolic acidosis, i.v. administration of bicarbonate results in a decrease of pH_i in brain, liver, skeletal muscle and red blood cells [6, 36, 37, 39, 44, 86, 103].

Diabetic ketoacidosis

Indications for the use of bicarbonate in diabetic ketoacidosis are currently less controversial than had previously been the case. There are reports of at least two studies in which the effects of bicarbonate on blood pH, glucose, bicarbonate and ketone concentrations were examined in patients with diabetic ketoacidosis [53, 63]. In general, it was found that administration of bicarbonate did not result in either a greater decrease in blood concentrations of ketone or a more rapid increase in blood pH than was observed in patients who did not receive bicarbonate. Thus sodium bicarbonate administered to patients with diabetic ketoacidosis had no apparent effect on the rate of change in pH, blood ketone concentrations, the change in blood concentration of bicarbonate or arterial P_{CO_2}. In addition, the ultimate survival rate was similar in patients who did or did not receive bicarbonate. Administration of sodium bicarbonate has been associated with an increase in spinal fluid P_{CO_2} which was not observed when bicarbonate was not given [8, 69]. This resulted in a small but significant decrease in the pH of cerebrospinal fluid. Earlier studies had suggested that such a decrease in spinal fluid pH secondary to administration of bicarbonate might lead to depression of the sensorium [79]. However, subsequent studies have failed to confirm these earlier impressions [76]. Although the reduction in spinal fluid pH may not be harmful, it is almost certainly of no benefit. Evidence that bicarbonate may be harmful to patients with ketoacidosis is found in other studies. In animals with metabolic acidosis, administration of bicarbonate decreased delivery of oxygen to the brain, increased cerebrospinal fluid concentrations of lactate and decreased brain intracellular pH [16, 86].

Another reason why the use of bicarbonate in patients with diabetic ketoacidosis may not be useful relates to the stoichiometry of the disorder. In ketoacidosis, there is at least 400–500 mmol of available endogenous bicarbonate precursor in the

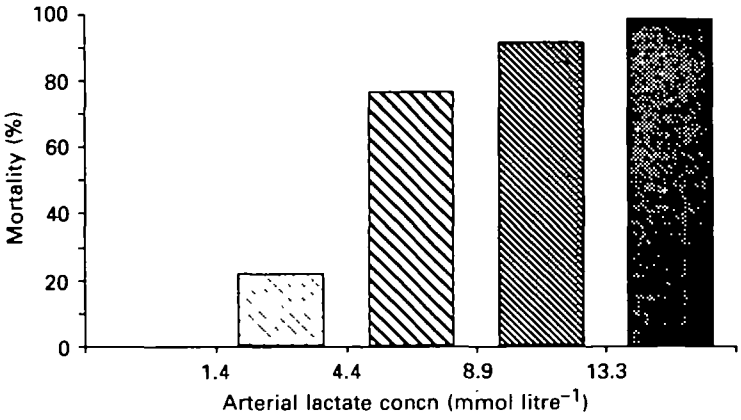

FIG. 2. Mortality of lactic acidosis as a function of the initial arterial concentration of lactate. There is an increasing mortality with increasing lactate concentration such that a value greater than 9 mmol litre^{-1} carries a mortality in excess of 90% [23, 75].

form of lactate and ketoacid anions. The liver is able to metabolize these anions, and for each 1 mmol metabolized, 1 mmol of H^+ ion is consumed and a bicarbonate ion is generated [10, 21]. Thus, in patients with diabetic ketoacidosis, the body has more than 400 mmol of available bicarbonate precursor, and with insulin administration, ketogenesis (a H^+ ion generating reaction) ceases. Administration of the 50–100 mmol of bicarbonate given commonly to patients with diabetic ketoacidosis would therefore not be expected to influence arterial pH and, in practice, it generally does not [63]. Overall, it appears that there are few if any beneficial effects attributed to the use of bicarbonate in patients with ketoacidosis, and there are several potentially harmful mechanisms. The clinical importance of these mechanisms remains to be established.

Lactic acidosis

Lactic acidoses is probably the most common form of metabolic acidosis and is generally defined as metabolic acidosis resulting from the accumulation of lactic acid, with blood lactate concentration in excess of 5 mmol litre^{-1} and blood pH less than 7.25. The mechanisms by which lactic accumulation occurs vary, and include both the stimulation of production of lactate and reduction in lactate metabolism. Clinically, disorders of lactate metabolism have traditionally been classified as either anaerobic (Type A) or aerobic (Type B) [22, 23]. The hallmark of Type A lactic acidosis is tissue hypoxia resulting in anaerobic lactic acid production. Such disorders include cardiopulmonary arrest and other states (such as shock, haemorrhage, pulmonary oedema) characterized by impaired cardiac performance, reduced tissue perfusion and arterial hypoxaemia. Type B lactic acidosis is not associated with tissue hypoxia, but there is increased production of lactic acid, for other metabolic reasons. Examples of Type B lactic acidosis include diabetes mellitus, certain malignancies and congenital disease of the liver which impair lactate metabolism. Of the two forms of lactic acidosis, Type A is more common clinically and generally is associated with a greater morbidity and mortality.

Hyperlactataemia is far more than an isolated laboratory finding. It has been observed consistently that when the blood concentration of lactate exceeds 9 mmol litre^{-1}, mortality exceeds 75% (fig. 2) [75]. This formulation excludes those clinical conditions in which lactate is acutely and reversibly increased, such as following grand mal seizures or strenuous anaerobic exercise [70].

Lactic acidosis and the cardiovascular system

Lactic acidosis appears to have negative effects on myocardial function which are both direct and indirect, and are present when the acidosis is caused by either hypercapnia with hypoxia or metabolic acidosis *per se* [47, 67, 97]. However, recent data strongly suggest that, after myocardial ischaemia (as a result of cardiac arrest or coronary occlusion), myocardial pH_i may decrease to less than 6.0 [51], not as a result of H^+ ions derived from myocardial lactate accumulation, but rather as a result of a combination of H^+ ion from the

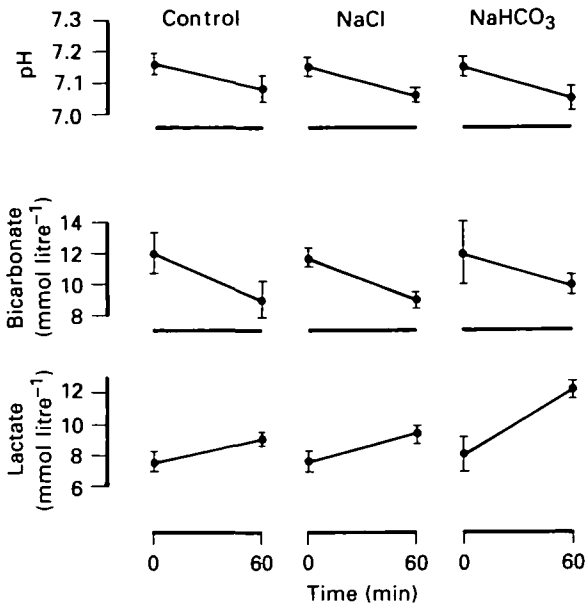

FIG. 3. Effects of i.v. bicarbonate ($NaHCO_3$) compared with saline (NaCl) or no therapy (control) in dogs with hypoxic lactic acidosis (arterial Po_2 less than 4 kPa). After administration of $NaHCO_3$, there is a continuous decline in both arterial blood pH and bicarbonate concentration, with an increase in lactate concentration. With equimolar NaCl, the changes in arterial blood pH and bicarbonate concentration are similar. (Figure from [39], by permission of *Science*.)

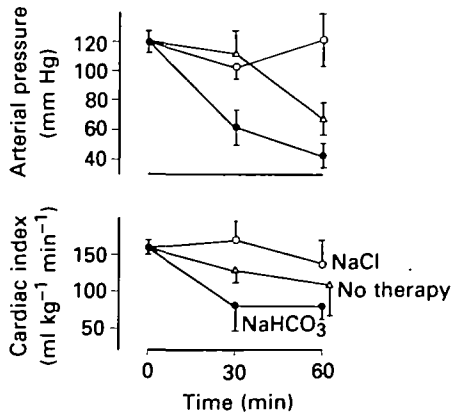

FIG. 4. Effects of i.v. sodium bicarbonate (●) compared with NaCl (○) or no therapy (△) in dogs with hypoxic lactic acidosis (arterial Po_2 less than 4 kPa). After administration of $NaHCO_3$, there is a steady decline in both arterial pressure and cardiac output, while with equimolar NaCl, there is no change. (Figure from [39], by permission of *Science*.)

hydrolysis of ATP [48, 105] and "metabolic" hypercapnia [50, 78, 97]. Furthermore, the acid–base status of the heart and coronary circulation is not accurately reflected by the arterial blood chemistry [1, 78]. Since effects on the myocardium are largely determined by myocardial pH_i and not the extracellular pH, it is not appropriate to administer sodium bicarbonate on the basis of arterial gases [100]. Nonetheless, the development of myocardial intracellular acidosis is known to be associated with depression of myocardial mechanical function [2, 61]. The goal of cardiopulmonary resuscitation has been to correct rapidly both hypoxia and metabolic acidosis, in order to promote the recovery of myocardial function. However, sodium bicarbonate has not been shown consistently to improve haemodynamics, increase arterial pH or increase the blood concentration of bicarbonate, and it appears to have adverse effects on both tissue oxygenation and myocardial function [26, 36, 39, 57, 91, 93].

Animal experiments have demonstrated that, in hypoxic metabolic acidosis, sodium bicarbonate neither increases arterial pH nor affects plasma bicarbonate concentration (fig. 3) [39]. As a consequence, administration of sodium bicarbonate to animals with hypoxic metabolic acidosis causes a decline in both systemic arterial pressure and cardiac output (fig. 4). Additionally, studies in several different animal models have confirmed that the administration of sodium bicarbonate in hypoxic states causes a reduction in tissue pH_i in liver, skeletal muscle, red cells and brain [6, 16, 37, 44, 103]. The mechanism of the reduction in pH_i has not been elucidated completely, but probably involves increased breakdown and decreased synthesis of ATP [48], increase in intracellular tissue concentration of lactic acid and increased tissue production of carbon dioxide [35, 40, 78]. Clinically, the mixed venous Pco_2 increases disproportionately in cardiac arrest [19, 100], causing severe venous acidosis which may not be reflected by arterial blood-gas analyses [1, 35]. In this setting, the administration of sodium bicarbonate may aggravate intracellular and extracellular acidosis by accelerating production of carbon dioxide [35, 40, 50, 77].

ALTERNATIVES TO SODIUM BICARBONATE

Possible detrimental effects of bicarbonate may be summarized as: venous hypercapnia, decrease in intracellular pH, cerebrospinal fluid acidosis, tissue hypoxia, circulatory congestion and hypernatraemia. Because of these varied effects on organ function (particularly that of the heart)

during hypoxic states, several other agents have been developed for the treatment of Type A lactic acidosis. The goal has been to improve the blood pH during hypoxic states without reducing oxygen delivery, stimulating production of carbon dioxide or lactate, or adversely affecting end organ function. The most promising of these agents are Tris buffer (2-amino-2-hydroxymethyl-1,3-propanediol) (THAM), Carbicarb and dichloroacetate. All have been tested in human subjects with metabolic acidosis but, as of March 1991, none has been approved for use in humans [11, 15, 24, 30, 93, 103].

Dichloroacetate

Sodium dichloroacetate (DCA) may be an effective and safe form of therapy for reducing lactate concentrations and increasing pH in lactic acidosis. The effects of this drug on intermediary metabolism have been studied extensively in normal animals and in several animal models of lactic acidosis [28, 74, 92]. In animals with increased lactate concentrations induced by exercise, diabetes, endotoxin, sepsis, phenformin, hepatic insufficiency, adrenaline or hypoxia, administration of DCA results in a reduction in the concentration. In dogs with lactic acidosis caused by hypoxia, diabetes or phenformin, i.v. administration of DCA improved both intracellular and systemic pH [38, 72].

To date, the effects of DCA in the treatment of lactic acidosis have been described in several clinical studies involving both adults and children [15, 27, 45, 46, 92–94]. More than 80% of the patients in these studies responded to treatment, defined by at least a 20% reduction in blood concentration of lactate occurring within 6 h of the first dose of DCA. Administration of DCA did not change the arterial or mixed venous P_{CO_2} values, and thus presumably does not result in intracellular accumulation of carbon dioxide [74, 93]. There have been no reported adverse effects of oral or parenteral administration of DCA in children or adults with lactic acidosis. Based on these preliminary data, a multi-centred, controlled clinical trial is currently in progress to evaluate the effect of DCA therapy on morbidity and mortality in adult patients with acquired causes of lactic acidosis [29]. Initial results from this study should become available within the next year.

In animal studies, dichloroacetate increases arterial pressure, cardiac output, oxygen delivery,

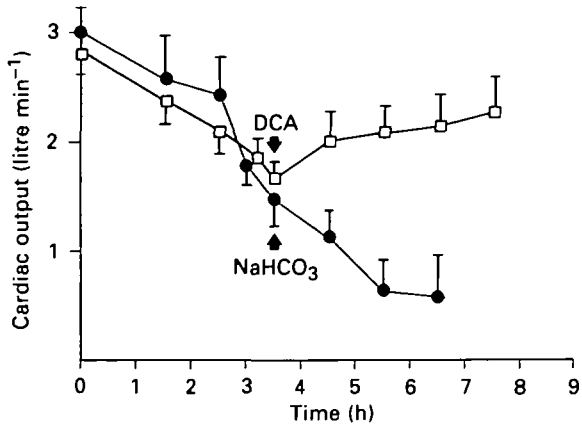

FIG. 5. Effects of i.v. sodium bicarbonate ($NaHCO_3$) (●) compared with that of dichloroacetate (DCA) (□) in dogs with phenformin-induced lactic acidosis [7]. With DCA, there is restoration of cardiac output to normal, while with bicarbonate the cardiac output declines to values incompatible with life. (Figure from [72], by permission of the *Journal of Clinical Investigation*.)

liver pH_i and liver uptake of lactate in dogs with either phenformin-induced [72, 74] or hypoxic [38] lactic acidosis (fig. 5). It is not known if DCA affects tissue oxygen extraction *in vivo* or if DCA alters myocardial pH_i; however, there is substantial improvement in myocardial performance following administration of DCA. Such effects include increased cardiac output and stroke work, myocardial efficiency index, and increased intramyocardial concentrations of ATP and improvement in the ECG [17, 62, 80, 98]. Clearly, the mechanisms by which DCA improves cardiovascular function in hypoxic lactic acidosis are complex. However, both in patients with lactic acidosis and in animal models with hypoxic lactic acidosis, administration of DCA improves cardiac output, while bicarbonate decreases both arterial pressure and cardiac output [38, 39, 72, 93]. It is clear that, in patients with lactic acidosis, DCA improves arterial blood-gas tensions and decreases blood lactate concentrations. Improved survival has not yet been demonstrated.

Carbicarb

Carbicarb was described in 1984 [32] as a potential replacement for sodium bicarbonate in the therapy of metabolic acidosis [52]. It is an equimolar solution of sodium bicarbonate and sodium carbonate [11]. It buffers acids in a similar manner to the action by sodium bicarbonate but

without increasing the blood concentration of carbon dioxide. This permits an evaluation of the hypothesis that generation of carbon dioxide after administration of sodium bicarbonate causes many of the detrimental effects on lactate metabolism and cardiovascular function [52]. Studies using sodium bicarbonate in an acidotic *in vitro* system demonstrate that bicarbonate will not increase the pH of blood when there are constraints to the removal of carbon dioxide from the system [71], such as in circulatory congestion or shock. In normal volunteers, administration of sodium bicarbonate resulted in a marked increase in excretion of carbon dioxide, whereas administration of Carbicarb resulted in a decrease in P_{CO_2} [85]. These results suggested that Carbicarb actually decreased generation of carbon dioxide when administered systemically.

Carbicarb was compared with sodium bicarbonate in rats with metabolic acidosis induced by asphyxia [96]. In rats with an arterial pH of 7.17, sodium bicarbonate did not increase arterial pH, but resulted in significant increases in both P_{CO_2} and lactate concentration. With Carbicarb, there was a significant increase in arterial pH, but no change in lactate concentration or P_{CO_2}. In another study, rats were made acidotic by either ammonium chloride or respiratory hypercapnia [86]. In the rats with ammonium chloride-induced acidosis, administration of sodium bicarbonate resulted in a decrement of brain pH_i with an increase of arterial P_{CO_2}. Carbicarb normalized arterial pH without an increase in arterial P_{CO_2}, and the pH_i of brain was alkalinized [86]. In the rats with respiratory hypercapnia, sodium bicarbonate intensified the hypercapnia. In a model of cerebral ischaemia, administration of sodium bicarbonate resulted in an increase in brain P_{CO_2} with a decline in brain pH_i [44].

In a laboratory study [11], 28 dogs with hypoxic lactic acidosis were treated with 2.5 mmol litre^{-1} kg^{-1} of either sodium bicarbonate or Carbicarb over 1 h. Measurements made after 1 h of hypoxia and then after 1 h of therapy comprised: cardiac haemodynamics, blood-gas tensions, liver pH_i, oxygen consumption and regional production of lactate. After treatment with Carbicarb, the arterial pH increased (from 7.22 to 7.27), but decreased after sodium bicarbonate (from 7.18 to 7.13). Mixed venous P_{CO_2} did not change with Carbicarb, but increased with sodium bicarbonate. Arterial lactate concentration stabilized with Carbicarb but increased with sodium bicarbonate. Use of lactate by muscle, gut and liver all improved with Carbicarb and decreased with sodium bicarbonate. Liver pH_i (normal = 6.99, hypoxia = 6.80) improved with Carbicarb (to 6.98), but decreased further with sodium bicarbonate (to 6.40). Muscle consumption of oxygen increased with Carbicarb, whereas it decreased with sodium bicarbonate. Arterial pressure decreased less and the cardiac output remained stable with Carbicarb, but decreased by 31% with sodium bicarbonate. Stroke volume also improved with Carbicarb without a change in pulmonary capillary wedge pressure, suggesting a beneficial effect on cardiac function. Thus administration of Carbicarb to dogs with hypoxic lactic acidosis results in improvement in the arterial blood-gas tensions, tissue pH_i, production of lactate and cardiac haemodynamics. The response to Carbicarb contrasts with the effects of sodium bicarbonate and may be related to reduced systemic generation of carbon dioxide by Carbicarb. Thus, in laboratory animals, Carbicarb appears to be superior to sodium bicarbonate for the treatment of hypoxic states with lactic acidosis. Clinical trials commenced in 1990.

THAM

THAM is a synthetic buffer which has been proposed for the treatment of metabolic and respiratory acidosis. Theoretically, it counteracts the effects of accumulation of carbon dioxide in respiratory acidosis [24] and has been shown also to be effective in the treatment of some forms of metabolic acidosis [54]. At physiological pH (7.38), THAM has a buffer capacity about the same as that of normal blood [54]. Unlike other buffers, such as bicarbonate, THAM penetrates cells and is an effective intracellular buffer. In dogs with metabolic acidosis, administration of sodium bicarbonate resulted in an increased extracellular pH (from 7.30 to 7.58), but no change in pH_i. However, with THAM, extracellular pH increased from 7.34 to 7.47, pH_i increased from 7.08 to 7.27, with an increase in intracellular bicarbonate from 11.6 to 21.4 mmol litre^{-1}. Thus, THAM readily penetrates certain cells and appears to be an effective intracellular buffer [82].

Studies have been carried out in isolated left ventricle preparations. Addition of THAM to the perfused left ventricle at physiological pH increased myocardial contractility during ischaemia [30]. However, without ischaemia, the inotropic

effect was of smaller magnitude. Thus, in *in vitro* studies, THAM exerts an inotropic effect on ischaemic myocardium [30]. In an animal model of cardiac arrest, THAM did not improve survival when compared with bicarbonate [77]; however, this may be attributable to the fact that, overall, the particular animal model in question is not readily amenable to resuscitation, whatever the therapeutic intervention [35, 49, 77].

In preliminary clinical studies, THAM was used in the treatment of six patients with severe diabetic ketoacidosis (mean arterial pH = 7.12, bicarbonate = 8.8 mmol litre^{-1}). In all cases, THAM corrected the metabolic acidosis within 4–12 h without obvious toxicity [79]. In additional preliminary studies in five patients with acidosis of renal failure, THAM was successful in increasing the arterial pH in all five patients, again without obvious toxicity [82]. Thus, based on the effects of THAM on ischaemic myocardium *in vitro* [30], and *in vivo* effects on metabolic acidosis of several different etiologies [81, 82], THAM may be a valuable agent for the overall management of patients with lactic acidosis or cardiac arrest. Studies have not yet been carried out in either human subjects or animal models of lactic acidosis or cardiac arrest.

THAM, DCA and Carbicarb appear to be promising agents for the management of metabolic acidosis. All have been used in human subjects without apparent toxicity. At this juncture, none is approved for human use. Based on data in both laboratory animals and patients with various forms of metabolic acidosis, all appear to be superior to sodium bicarbonate in the management of metabolic acidosis, and it is hoped that these agents will be available for human use in the near future.

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