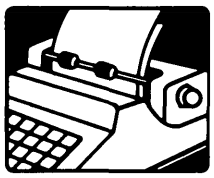
Editorial



Lactic Acidosis: High-Dose or Low-Dose Bicarbonate Therapy?

Current clinical convention dictates that patients with life-threatening lactic acidemia should receive high doses of intravenous sodium bicarbonate.[1-6] Consideration of the metabolic effects of exogenous bicarbonate on acid-base status, however, tends to cast doubt on the wisdom of this dogma. The equilibrium

$$H_2O + CO_2 \rightleftarrows H_2CO_3 \rightleftarrows H^+ + HCO_3^-$$

occurs intracellularly, extracellularly, and in the cerebrospinal fluid (CSF). Adding sodium bicarbonate to the extracellular fluid causes a decrease in hydrogen ions with subsequent increase in carbon dioxide (CO_2) concentration. Since CO_2, but not bicarbonate, readily diffuses across cell membranes and into the CSF, this leads to an increase in intracellular and CSF CO_2 concentration, with consequent rise in hydrogen ion concentration. Thus sodium bicarbonate, though causing an increase in pH extracellularly, also results in a decrease in pH intracellularly and in the CSF. Support for this hypothesis comes from studies on skeletal muscle,[7-10] heart muscle,[10,11] liver, [7,12] erythrocytes,[12] and CSF.[13-16] While acid-base balance is normally restored via increased respiratory CO_2 excretion,[17] intracellular and CSF acidosis may persist if the rate of bicarbonate administration exceeds the rate of CO_2 excretion. In this context it is important to note that sodium bicarbonate therapy in metabolic acidosis has been associated with the onset of stupor,[15,16] and that severe lactic acidosis may itself culminate in respiratory failure.[18]

Among the major arguments put forward in favor of the use of high-dose sodium bicarbonate therapy have been that metabolic acidosis in the perfused rat liver severely impairs hepatic lactate metabolism,[19,20] and that metabolic acidosis can result in a negative inotropic effect.[21,22] However, both these effects are thought to be mediated by intracellular acidosis[19,22,23] and indeed hepatic intracellular acidosis is postulated as a fundamental factor in the pathogenesis of some types of lactic acidosis.[24] Thus if, as postulated, high-dose sodium bicarbonate causes intracellular acidosis, it would be expected to worsen rather than improve hepatic lactate metabolism and cardiac output in lactic acidosis. Animal experiments are in support of this view. When given to animals with lactic acidosis, sodium bicarbonate causes increasing lactic acidemia, a fall in intracellular pH, cardiovascular collapse, and sometimes increased mortality.[7,12] Infused sodium bicarbonate has been used in the induction and maintenance of lactic acidosis in the diabetic rabbit.[25] Infusion of bicarbonate in the ketoacidotic rat produces signs of tissue anoxia and a three- to fourfold rise in blood and liver lactate concentrations.[26] Conversely, when the experiments on the effect of metabolic acidosis on the perfused rat liver were recently repeated under conditions of simulated partial respiratory compensation of metabolic acidosis no effect of acidosis on hepatic lactate metabolism was found.[27] It is considered that the low PCO_2 of the perfusate in these experiments drew readily diffusable CO_2 out of the hepatic cells, shifting the intracellular bicarbonate equilibrium to the left to compensate for the acidosis and allow hepatic lactate metabolism to continue normally.

Controlled studies in human patients, similar to those performed in animals, are clearly not practical. In practice retrospective analysis of the case report literature is the main source of patient information. High-dose sodium bicarbonate therapy has previously appeared to receive support from a retrospective analysis of biguanide-induced lactic acidosis case reports suggesting that patients whose arterial pH was deliberately restored to normal within 2–6 h, and kept there, fared considerably better than those in whom partial or no correction was achieved.[28] However, in this study, the relationship between survival and arterial pH was clearer than a relationship between arterial pH and bicarbonate therapy or survival and bicarbonate therapy. Obviously the pH would return to normal in survivors as the authors have later accepted,[22] making it difficult to come to a satisfactory conclusion. A study from France of 18 patients found that comparable amounts of sodium bicarbonate were given to those who died and those who survived but both groups were given

"large amounts."[29] In 1978 a world-wide study of all reported cases of biguanide-induced lactic acidosis found no significant difference between the doses of sodium bicarbonate given to patients who died and those who survived.[30] The average dose of sodium bicarbonate given in the first 24 h was 534 mmol, demonstrating widespread use of high-dose treatment.

Re-examination of this case report literature today in the light of the theory that high-dose sodium bicarbonate causes intracellular acidosis reveals that the deleterious effects of this treatment predicted by animal experiments have indeed occurred frequently in patients. An increase in lactate,[31-42] hypotension,[40-46] pulmonary edema,[41-43,46-49] and a decrease in consciousness[35,41] and persisting coma[36-39] have all been seen after high-dose bicarbonate therapy in patients with biguanide-induced lactic acidosis. The possibility emerges that high-dose sodium bicarbonate may have contributed (perhaps to a considerable extent) to the high mortality associated with lactic acidosis.

Nevertheless, having acknowledged the danger of high-dose sodium bicarbonate the problem remains that acidosis per se may have adverse effects.[50] In view of this there remains a case in lactic acidosis, as in diabetic ketoacidosis, for treating the acidosis per se when it is of extreme degree. If sodium bicarbonate is to be used at all, a more cautious approach is clearly indicated. Kassier has argued that raising plasma bicarbonate by 4–6 mmol/L with sodium bicarbonate is adequate to avert the dangers of extreme acidosis as long as respiratory compensation continues, and that further treatment is then only required to raise plasma bicarbonate to 14 or 16 mmol/L over the next 24 h.[51] As with high-dose bicarbonate therapy evaluation of the efficacy of such an approach is difficult. As far as biguanide-induced lactic acidosis is concerned there are recorded cases of patients receiving comparatively small amounts of sodium bicarbonate and most of these survived.[18,40,43,52-55] Though it could be argued that many of them did not have severe lactic acidosis, there are examples of extremely severe lactic acidosis being treated successfully with lower-dose therapy.[4,52] Indeed, Matz found that six of seven patients with lactic acidosis survived without any sodium bicarbonate and concluded that "large amounts of bicarbonate in the therapy of acidosis is an entrenched medical myth";[56,57] and others have had the same experience.[58]

The traditional "chemical" approach to the treatment of lactic acidosis, which aimed at total rapid correction of acidosis by a dose of sodium bicarbonate calculated according to the base deficit, should be replaced by a more rational "physiologic" approach. Treatment should first aim at ensuring that adequate respiratory compensation of metabolic acidosis is taking place. If not, as may be the case in the comatosed or semi-comatosed patient, respiratory stimulants or artificial ventilation should be commenced to bring PCO_2 to low levels. This respiratory compensation should restore hepatic intracellular pH and ensure that hepatic lactate metabolism proceeds.[27] It will also tend to restore cardiac intracellular pH and therefore tend to counteract the negative inotropic effect of metabolic acidosis. Any depletion of circulating fluid volume should be corrected and cardiac output then increased further, if necessary, with appropriate positive inotropic agents, thereby ensuring the good hepatic perfusion essential for hepatic lactate metabolism.[59,60] If acidosis is very severe (pH < 7.0) correction should not be rapid and sodium bicarbonate, if used, should be given with caution and only when hyperventilation is sufficient to remove the excess CO_2 thus generated. The approach to bicarbonate therapy should be along the lines of that now recommended for diabetic ketoacidosis.[61] The treatment should aim to correct base deficit by only 4–6 mmol/L initially.[51] As a rule of thumb, twice the body weight in kilograms gives the value of the appropriate number of millimoles of bicarbonate to be infused over the first hour. Further small doses of bicarbonate could then be given intermittently, if essential, in order to raise the plasma bicarbonate to 14 or 16 mmol/L over the next 24 h.[51] In biguanide-induced cases, if worsening lactic acidosis is occurring despite these measures, particularly with overdosage when high levels of biguanide may persist, dialysis should be considered and possibly glucose and insulin. The place of dichloroacetate, which has proved beneficial in animals[62] and man,[63] and tromethamine (THAM), which raises intracellular as well as extracellular pH,[64] warrants further evaluation.

Although much of the above discussion focuses on lactic acidosis associated with biguanide therapy (type B2), the fundamental importance of ensuring adequate respiratory compensation to correct intracellular acidosis and the danger of sodium bicarbonate administration without sufficient hyperventilation to remove the CO_2 generated apply equally to lactic acidosis in cardiac arrest and shock (type A), and indeed to all forms of metabolic acidosis.

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