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Effects of bicarbonate therapy on hemodynamics and tissue oxygenation in patients with lactic acidosis: A prospective, controlled clinical study

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Objective: **To determine whether correction of acidemia using bicarbonate improves hemodynamic variables and tissue oxygenation in patients with lactic acidosis.**

Design: **Prospective, randomized, blinded, cross over study. Each patient sequentially received sodium bicarbonate and sodium chloride. The order of the infusions was randomized.**

Patients: **Ten patients with metabolic acidosis, increased arterial plasma lactate concentrations (>2.45 mmol/L), and no severe renal failure (creatinine <250 μmol/L [<2.3 mg/dL]).**

Method: **Sodium bicarbonate (1 mmol/kg body weight) or equal volume of sodium chloride was injected iv at the beginning of two successive 1-hr study periods. Period order was randomized. Arterial and venous blood gas measurements, plasma electrolytes (sodium, potassium, chloride), osmolality and lactate, 2,3-diphosphoglycerate (DPG), and oxygen hemoglobin affinity, hemodynamic variables, oxygen delivery, and oxygen consumption measurements were obtained before and repeatedly during the 1-hr period after the injection of bicarbonate or sodium chloride.**

Measurements and Main Results: **Sodium bicarbonate administration increased arterial and venous pH, serum bicarbonate, and the partial pressure of CO_2 in arterial and venous blood. Hemodynamic responses to sodium bicarbonate and sodium chloride were similar. Tissue oxygenation (as estimated by oxygen delivery, oxygen consumption, oxygen extraction ratio, and transcutaneous oxygen pressure) was not modified. No changes in serum sodium concentration, osmolality, arterial and venous lactate, red cell 2,3-DPG levels, or hemoglobin affinity for oxygen were observed.**

Conclusion: **Administration of sodium bicarbonate did not improve hemodynamic variables in patients with lactic acidosis, but did not worsen tissue oxygenation. (Crit Care Med 1991; 19:1352)**

KEY WORDS: **lactic acidosis; bicarbonate; hemodynamics; shock, septic; intensive care unit; cardiac output; oxygen consumption; pH; blood gas analysis**

Bicarbonate has been used in the treatment of various forms of lactic acidosis for at least 30 yrs (1, 2). However, growing clinical and experimental evidence (3–6) indicates that reliance on alkali therapy for lactic acidosis may be ill advised.

Data from both human and animal investigations suggest that alkali administration may actually be deleterious in the treatment of lactic acidosis. Some of the more important potential adverse actions of bicarbonate therapy include hypercapnia and aggravation of intracellular acidosis (7, 8), hyperosmolality (9), and a detrimental effect on cardiac function (10). Sodium bicarbonate administration increases the affinity of hemoglobin for oxygen. This effect, combined with the already reduced erythrocyte 2,3-diphosphoglycerate (2,3-DPG) levels produced by acidosis, further compromises tissue oxygen delivery (11). Data (3, 4) suggest that sodium bicarbonate administration leads to markedly decreased hepatic portal vein blood flow, increased gut lactate production, and increased blood lactate concentrations.

We hypothesized that sodium bicarbonate therapy may have negative hemodynamic effects and may decrease oxygen delivery when it is used to treat patients who have lactic acidosis. To test this hypothesis, we performed a prospective, randomized,

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placebo-controlled trial in order to evaluate the effect of bicarbonate therapy on hemodynamics and oxygen delivery in patients with lactic acidosis.

MATERIALS AND METHODS

Patients. Ten critically ill patients in the ICU of Calmette Hospital, Lille, France, were studied according to a protocol approved by the Human Ethic Committee of the Lille University Hospital. Informed consent was waived.

Patients who had clinically indicated, indwelling pulmonary and systemic arterial catheters, were studied if they had a metabolic acidosis (arterial bicarbonate concentration <22 mmol/L) and an increased arterial plasma lactate concentration (>2.45 mmol/L). Patients with severe renal dysfunction (serum creatinine >250 μmol/L [>2.8 mg/dL]) were excluded. All patients were mechanically ventilated and ventilator settings provided a $Paco_2$ of up to 35 torr (4.6 kPa). All ten patients were receiving iv infusions of dopamine, dobutamine or a combination of the two.

Methods. We attempted to avoid patient variability and studied all patients after their hemodynamic status had stabilized. Ventilator settings and fluid infusion rates were kept constant during the study. No new medication was administered.

Alkalinization challenge was done by sodium bicarbonate (0.7 M, 1 mmol/kg body weight, i.e., 1.2 mL/kg) infused by a pump (0.5 1 mL/sec) via a central catheter.

Control injection was done by sodium chloride (0.75 M, 1 mmol/kg body weight diluted to achieve a volume of 1.2 mL/kg) infused following the same conditions.

The study included two periods separated by a 30-min interval to allow the patient's status to return to baseline. Each period included infusion of one of the two solutions and a 1-hr observation time. Measurements were done immediately before infusion and then 5, 15, 30, and 60 mins after.

The period order was randomized and each period received either bicarbonate infusion or sodium chloride infusion first. The total study duration for each patient was actually 2.5 hrs.

We measured arterial and mixed venous blood gases, bicarbonate, plasma lactate, serum osmolality, and sodium concentrations. We measured red cell 2,3-DPG and we determined hemoglobin affinity by a mixing technique and results were expressed as the partial pressure of oxygen at half-saturation (P_{50}) at 37°C, plasma pH, and using standard Bohr effect correcting factor.

End-tidal CO_2 was monitored (Capnolog, Draeger, Lubeck, FRG). The CO_2 production ($\dot{V}co_2$) was determined by measuring the area under the curve of instantaneous expired CO_2 concentration as the function of expired volume with a planimetric technique.

Continuous transcutaneous oxygen pressure was recorded from a transcutaneous monitor (Kontron, Basel, Switzerland) with a miniature Clark's electrode placed on the subclavian area. The electrode was heated and maintained at 44°C during the study.

Hemodynamic measurements included determination of mean arterial pressure, pulmonary artery pressures, pulmonary artery occlusion pressure, heart rate, and cardiac output using the thermodilution technique. Cardiac output was measured in triplicate using 1-mL injections of 5% dextrose in water at room temperature and a cardiac output computer (Baxter Edwards Critical-Care, Irvine, CA). Oxygen delivery ($\dot{D}o_2$), oxygen consumption ($\dot{V}o_2$), and oxygen extraction ratio were calculated using standard formulas (12).

Data Analysis. Analysis of variance was used for statistical analysis. The data were statistically evaluated by ANOVA for repeated procedures. Statistical analysis of data was performed using the Stat graphics statistical software package. The Student's *t*-test for paired samples was used for comparison between each group, with $p < .05$ determined as statistically significant. The data were expressed as mean ± SD.

RESULTS

Ten patients who had lactic acidosis were included in the study (Table 1). They were all medical patients with acute circulatory problems. No renal dysfunction existed the day before the study (mean creatinine concentration 110 ± 32 μmol/L [1.0 ± 0.3 mg/dL]). At the beginning of the study, no patient had severe renal dysfunction (creatinine 198 ± 42 μmol/L [2.2 ± 0.01 mg/dL]), plasma lactate was 7.6 mmol/L, and the baseline $Paco_2$ was 42 ± 5 torr (5.6 ± 0.7 kPa).

Four patients received sodium bicarbonate first and six patients received sodium chloride first. In the study, the dose of sodium bicarbonate used (1 mmol/kg) was actually adequate to improve acidemia throughout the study period. During the sodium bicarbonate infusion, the mean arterial pH, the mean serum bicarbonate, the mean $Paco_2$ and carbon dioxide tension in mixed venous blood increased significantly at 5, 15, 30, and 60 mins and $\dot{V}co_2$ increased significantly at 5 and 15 mins after bicarbonate administration (Fig. 1).

Serum sodium level and osmolality, arterial and venous lactate level, red cell 2,3-DPG, and

hemoglobin affinity for oxygen remained unchanged (Table 2).

There was no difference at any time between the effects of sodium bicarbonate (0.7 M, 1 mmol/kg body weight) and sodium chloride (0.75 M, 1 mmol/kg body weight) infusion on cardiac output, BP, pulmonary arterial pressure or pulmonary artery occlusion pressure (Table 3). $\dot{D}o_2$, $\dot{V}o_2$, and oxygen extraction ratio did not change significantly during the sodium bicarbonate infusion at 5, 15, or 60 mins. At 30 mins after sodium bicarbonate infusion, oxygen extraction ratio increased significantly and mixed venous oxygen saturation decreased significantly (Table 3).

During sodium chloride infusion, no change occurred for any variable.

DISCUSSION

Many clinicians believe that correction of acidemia, using sodium bicarbonate therapy improves hemodynamics (13, 14), increases cardiovascular response to circulating catecholamines (15), and improves lactate metabolism (16). An arterial pH of 7.20 is often the point at which sodium bicarbonate therapy is recommended (17, 18).

However, both clinical and laboratory studies (3–6) suggest that bicarbonate may be of no benefit or may actually be harmful under circumstances, such as lactic acidosis. In different laboratory studies (4) using experimental models of lactic acidosis (i.e., lactic acidosis due to either hepatectomy, hypoxia, lactic acid infusion or phenformin), iv administration of sodium bicarbonate worsens rather than alleviates the metabolic and hemodynamic consequences of lactic acidosis (i.e., cardiac output, tissue

Table 1. Characteristics of ten patients who had lactic acidosis

Patient	Sex	Age (yr)	Diagnosis	Outcome
1	Male	76	Pneumonia, septic shock	Died
2	Male	75	Pneumonia septic shock	Died
3	Male	70	Pneumonia septic shock	Died
4	Female	65	Septic shock	Died
5	Male	65	Septic shock	Died
6	Male	60	Septic shock	Survived
7	Male	63	Pneumonia septic shock	Died
8	Male	61	Cardiac failure	Died
9	Female	72	Ischemic bowel, septic shock	Died
10	Male	74	Cardiac failure	Died

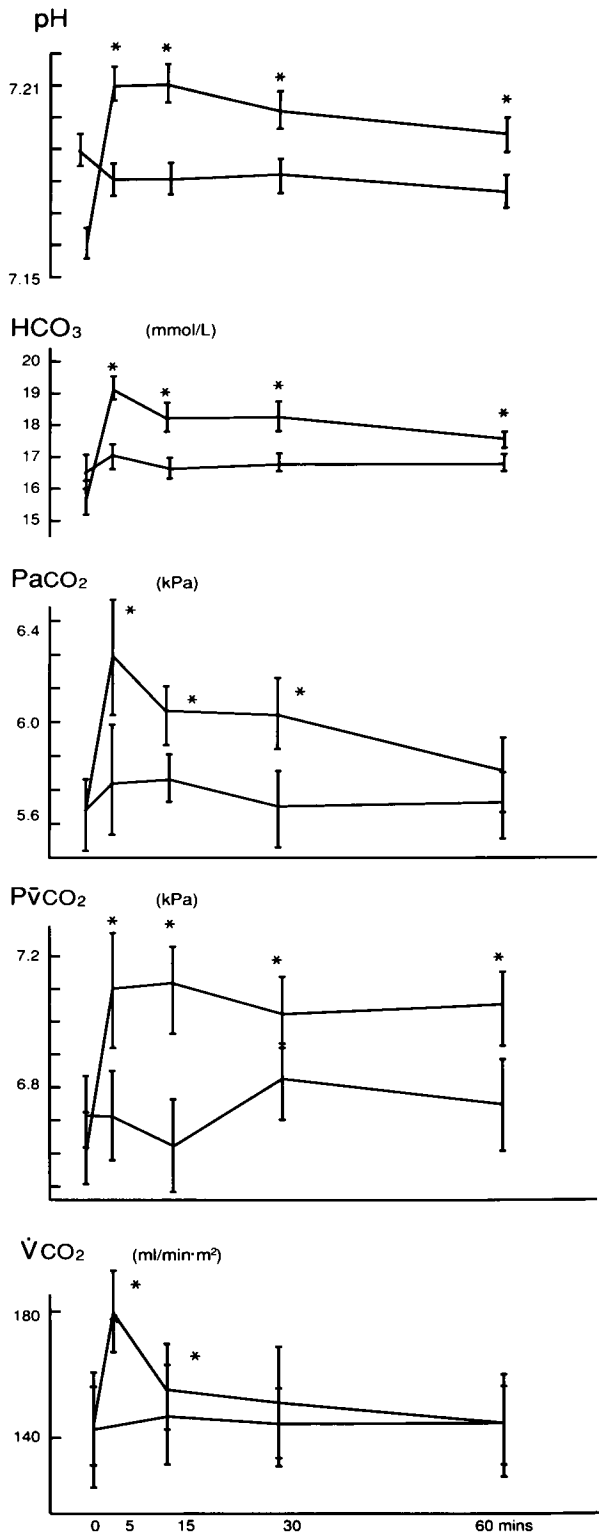

Figure 1. Arterial pH, bicarbonate (HCO_3), $Paco_2$, carbon dioxide tension in mixed venous blood ($P\bar{v}co_2$), and CO_2 production ($\dot{V}co_2$) before and at 5, 15, 30, and 60 mins after sodium bicarbonate infusion (*up*) and sodium chloride infusion (*down*) (mean ± SD values). *$p < .01$ compared with time 0. To convert kPa to mm Hg, multiply the value by 7.50.

Table 2. Change in serum sodium concentration, osmolality, arterial and venous lactate levels, 2, 3-DPG, and oxygen hemoglobin affinity during sodium bicarbonate and sodium chloride infusions. All values are expressed as mean ± SD. No statistical difference was observed

	HCO_3			NaCl		
	T_0	30 Mins	60 Mins	T_0	30 Mins	60 Mins
Sodium (mmol/L)	135 ± 9	137 ± 8	137 ± 8	136 ± 10	137 ± 8	137 ± 9
Osmolality (mosm/kg)	323 ± 14	325 ± 13	326 ± 14	324 ± 17	326 ± 19	327 ± 17
Arterial lactate (mmol/L)	7.6 ± 8.7	8.2 ± 9.6	7.5 ± 8.1	7.5 ± 8.1	7.6 ± 8.3	7.4 ± 8.0
Venous lactate (mmol/L)	7.4 ± 8.2	8.1 ± 9.6	7.9 ± 8.3	7.5 ± 8.4	7.6 ± 8.6	7.5 ± 8.3
2,3 DPG (g/L)	0.31 ± 0.10	0.27 ± 0.06	0.32 ± 0.10	0.31 ± 0.10	0.30 ± 0.10	0.32 ± 0.10
Oxygen hemoglobin affinity (P_{50}) (kPa)	3.1 ± 0.2	3.1 ± 0.2	3.1 ± 0.2	3.1 ± 0.1	3.1 ± 0.2	3.1 ± 0.2

HCO_3, bicarbonate; NaCl, sodium chloride; 2,3-DPG, 2,3-diphosphoglycerate.
T_0, 5 mins before the infusion; 30 mins, 30 mins after the infusion; 60 mins, 60 mins after the infusion.

Table 3. Hemodynamic variables, oxygenation variables, arterial and venous oxygen saturation, and transcutaneous oxygen pressure change during sodium bicarbonate and sodium chloride infusions (mean ± SD)

	$NaHCO_3$ Infusion			NaCl Infusion		
	T_0	30 Mins	60 Mins	T_0	30 Mins	60 Mins
MAP (mm Hg)	68 ± 17	66 ± 16	64 ± 14	64 ± 14	62 ± 14	62 ± 14
MPAP (mm Hg)	34 ± 6	32 ± 8	31 ± 9	31 ± 8	31 ± 8	30 ± 8
PAOP (mm Hg)	13 ± 4	14 ± 4	15 ± 5	13 ± 6	14 ± 6	13 ± 6
Cardiac index (L/min·m²)	3.3 ± 1.6	3.2 ± 1.6	3.2 ± 1.8	3.2 ± 1.8	2.9 ± 1.9	2.9 ± 1.5
$\dot{D}o_2$ (mL/min·m²)	514 ± 234	495 ± 224	498 ± 254	469 ± 265	434 ± 224	451 ± 234
$\dot{V}o_2$ (mL/min·m²)	119 ± 59	132 ± 60	120 ± 61	117 ± 65	116 ± 63	117 ± 62
Oxygen extraction ratio (%)	26.4 ± 13.2	29.4 ± 10.4[a]	27.9 ± 11.8	28.7 ± 11.3	30.0 ± 12.0	29.5 ± 11.6
Sao_2 (%)	91.9 ± 5.0	91.8 ± 5.0	92.3 ± 4.0	89.8 ± 7.0	92 ± 5.0	92.1 ± 4.0
$S\bar{v}o_2$ (%)	69 ± 16	66 ± 13[a]	68 ± 14	67 ± 14	67 ± 14	67 ± 13
$Ptco_2$ (kPa)	6.6 ± 2.8	8.8 ± 6.0	8.8 ± 5.6	5.8 ± 3.4	6.4 ± 3.2	5.6 ± 3.1
(torr)	50 ± 21	66 ± 45	66 ± 42	44 ± 26	48 ± 24	42 ± 23

[a] $p < .01$ compared with time 0.
$NaHCO_3$, sodium bicarbonate; NaCl, sodium chloride; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; PAOP, pulmonary artery occlusion pressure; CI, cardiac index; $\dot{D}o_2$, oxygen delivery; $\dot{V}o_2$, oxygen consumption; Sao_2, arterial oxygen saturation; $S\bar{v}o_2$, mixed venous saturation; $Ptco_2$, transcutaneous oxygen pressure.
T_0, 5 mins before the infusion; 30 mins, 30 mins after the infusion; 60 mins, 60 mins after the infusion.

oxygenation, extracellular and intracellular pH, lactate metabolism) (8). In patients with metabolic acidosis treated with sodium bicarbonate, intracellular and hyperosmolar state may occur (9), and the hemoglobin affinity for oxygen may increase, further compromising oxygen delivery because of the already reduced 2,3-DPG erythrocyte concentration produced by acidosis (11).

With this study, we sought an answer to three questions: a) Does bicarbonate infusion increase arterial pH concentrations in patients with lactic acidosis? b) Does correction of acidemia using sodium bicarbonate improve hemodynamics? c) Does tissue oxygenation change with correction of pH?

In these ten critically ill patients with lactic acidosis, the sodium bicarbonate infusion increased arterial and venous pH and the serum bicarbonate concentration. These changes were associated with concomitant increases in $Paco_2$ and in carbon dioxide tension in mixed venous blood. The final change in arterial pH was the result of the net effect of the increase in serum bicarbonate and the accumulation of CO_2 generated during the buffering process. Another factor that may have contributed to the arterial pH change could be a modification in the rate of lactic acid production and its extraction by the liver. The lack of change in serum lactate concentrations makes increased lactate production

an unlikely factor contributing to the arterial pH change.

In these ten critically ill patients, the increase in arterial pH after bicarbonate infusion did not lead to increases in cardiac output, BP, or other hemodynamic variables.

Variability in the actions of sodium bicarbonate therapy both on hemodynamic and acid-base variables have been demonstrated. Thus, we are cautious when interpreting the findings from only ten patients, although the study of Cooper et al. (20) led to the same conclusions.

Another potential deleterious effect of sodium bicarbonate therapy is the modification of peripheral tissue oxygenation. We observed no change in hemoglobin oxygen affinity and 2,3-DPG measurements during sodium bicarbonate infusion. Tissue oxygenation variables, such as oxygen delivery, oxygen consumption, and oxygen extraction ratio, were not changed at 5, 15, or 60 mins following the initiation of sodium bicarbonate infusion. At 30 mins, the oxygen extraction ratio increased. At the same time, we observed an increase of transcutaneous oxygen pressure. So, although we are reluctant to interpret this difference, we can conclude that, at least, tissue oxygenation is not decreased during sodium bicarbonate infusion.

Eight of the ten patients were septic. Because sepsis unpredictably affects tissue oxygenation variables, we rigorously avoided patient variability and studied all patients after stabilization of their hemodynamic status. For the same reason, ventilator settings and fluid infusion rates were kept constant during the short study period. The fact that neither oxygen consumption nor oxygen delivery varied during the sodium chloride infusion confirmed this stability and demonstrated the lack of decrease in tissue oxygenation during bicarbonate infusion.

Our study confirmed that sodium bicarbonate infusion was ineffectual regarding hemodynamic state in ten patients with lactic acidosis, but, at the dose used in our study, bicarbonate did not worsen tissue oxygenation.

We speculate that the respiratory effect of the sodium bicarbonate infusion may override the beneficial effect that pH correction may have on hemodynamics.

Although we were not able to prove that increasing arterial pH in lactic acidosis is of much clinical value, other alkali agents may have differing actions.

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