Treatment of Severe Lactic Acidosis with Dichloroacetate

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Four patients with severe lactic acidosis associated with septic shock were treated with sodium dichloroacetate (DCA) (50 mg/kg body wt), an activator of pyruvate dehydrogenase. All patients were in a group with an expected mortality rate of 90–100%, based on previous studies. In one patient, treatment with DCA was associated with a decrease in blood lactate levels from 11.2 mM before treatment to 0.8 mM 16 h later. Markedly elevated blood pyruvate and alanine levels also decreased to normal. After treatment, the arterial blood pH rose to 7.53, and vasopressor agents were no longer needed to support blood pressure. Some degree of biochemical improvement was also noted in the other cases in whom the blood lactate levels before treatment were 15, 17, and 31 mM. However, all three patients eventually died of refractory acidosis. DIABETES CARE 5: 391–394, JULY–AUGUST 1982.

Lactic acidosis is a frequently fatal disorder that occurs in patients treated with biguanide hypoglycemic agents and in patients with shock, sepsis, leukemias, hepatic failure, and numerous other conditions. Occasionally no cause can be identified. Although many different treatments have been tried, none has proven successful when treatment of the underlying disease is not effective.

Sodium dichloroacetate (DCA) is a compound that decreases blood lactate concentrations in animals and man by activating pyruvate dehydrogenase in extrahepatic tissues, thus decreasing the release of pyruvate, lactate, and alanine into the circulation[1–5] (Figure 1). It is effective in the treatment of lactic acidosis associated with the administration of biguanides to experimental animals,[6–9] and lowers both lactate and mortality in experimental endotoxin shock.[10] For these reasons, investigation of its efficacy in the treatment of lactic acidosis has been advocated.[11–15] We describe here the metabolic effects of intravenous DCA in four patients with lactic acidosis related to septicemia. Since our trial began in 1977, shortly before phenformin was removed from the United States market, there have been no cases of biguanide-related lactic acidosis at our institution.

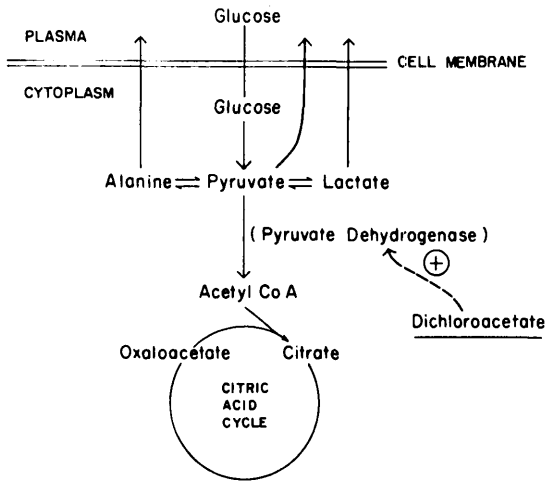

FIG. 1. Site of action of DCA in mammalian cells. DCA activates pyruvate dehydrogenase, thereby increasing the flux of 3-carbon compounds into the tricarboxylic acid cycle and decreasing the release of lactate, pyruvate, and alanine into the circulation.

METHODS

Dichloroacetate. Dichloroacetic acid (more than 99% pure) was obtained from Tokyo Kasei Kogyo Co., Ltd. (Tokyo, Japan). It was neutralized with 0.1 N NaOH to pH 7.4, sterilized, and packaged in the hospital pharmacy in normal saline at a final concentration of 20 mg/ml. Samples of this preparation were shown to be sterile and nonpyrogenic by standard criteria. The solution remained more than 99% pure after a year of storage at 24°C, as determined by gas

chromatograph-linked mass spectroscopy (kindly performed by Dr. Catherine Costello, Department of Chemistry, Massachusetts Institute of Technology).

Metabolite assays. Blood samples (7 ml) were drawn from a central venous or arterial cannula and immediately deproteinized in 7 ml of ice-cold 10% (w/v) perchloric acid. The acid extracts were centrifuged. Then the supernatants were neutralized and used for the following enzymic assays performed by standard methods;[1] lactate, pyruvate, alanine, glycerol, 3-hydroxybutyrate, and acetoacetate.

Study protocol. The study was approved by the Subcommittee for Human Studies of the Massachusetts General Hospital. Patients with lactic acidosis were candidates for the study if they had continued acidemia despite supportive measures and bicarbonate administration. Criteria for entry into the study included: arterial blood pH of less than 7.2; arterial blood pCO_2 of less than 45; serum bicarbonate concentration of less than 10 meq/L; a serum nitroprusside reaction that was not strongly positive; the absence of a history of ingestion of a substance known to cause an anion-gap metabolic acidosis; and the absence of severe renal failure. Patients with cardiogenic shock or shock due to a surgical emergency (e.g., massive trauma or ischemic bowel) were also excluded. Patients meeting these criteria received a 30-min infusion of DCA (50 mg/kg intravenously). If no improvement in their clinical status or arterial blood pH occurred, they received a second infusion 4 h after completion of the first dose. Blood metabolites and arterial blood pH were measured at frequent intervals following the infusions. Informed consent was obtained from the families of all patients before the administration of DCA.

RESULTS

Case Reports

Case 1. The patient was a 64-yr-old white man with abdominal pain, fever, and rigors; blood cultures obtained at this time grew *Klebsiella pneumoniae.* Antibiotic treatment was begun, but two days later he developed hypotension and Kussmaul respirations, and became obtunded. An arterial blood gas study 7 h before treatment with DCA and after approximately 310 meq of sodium bicarbonate revealed a pO_2 80, pCO_2 33, pH 7.17. Serum electrolytes were sodium 136, potassium 5.8, chloride 93, and CO_2 10 meq/L at that time. Liver function tests included total bilirubin 7.8 mg/dl (normal less than 1), alkaline phosphatase 64 IU/L (normal 13–39), lactate dehydrogenase 3760 U/ml (normal 60–120), and SGOT 3310 U/ml (normal 10–40). Hypoglycemia was further evidence of acute hepatic dysfunction, with blood glucose levels decreasing to as low as 27 mg/dl.

At the time DCA was administered, the patient was considered unsuitable for surgical exploration because of refractory hypotension and disseminated intravascular coagulation. His blood pressure was supported by norepinephrine (7 μg/min) and dobutamine (1000 μg/min). Mechanical ventilation was instituted and continued during the period of metabolic investigation. He received 3.5 g DCA over 30 min (50 mg/kg); 8 h later, the arterial blood values were pO_2 92, pCO_2 32, and pH 7.53, and plasma CO_2 was 18 meq/L. The alkalosis was presumably due to mechanical hyperventilation, since no further bicarbonate was administered after DCA treatment. Twenty-four hours later, his blood pressure was stable without vasopressor agents. His clinical improvement 4 h after DCA administration was such that the second infusion was felt not to be justified. Mechanical ventilation was discontinued the following day.

Case 2. The patient was a 55-yr-old Chinese man with severe, widespread amyloidosis and profound staphylococcal sepsis with severe hypotension. At the time DCA treatment was begun, he had received intravenous sodium bicarbonate therapy for 10 h and peritoneal dialysis against a bicarbonate (34 meq/L) bath. The systolic blood pressure was 74 mm Hg despite the intravenous infusion of dopamine (1000 μg/min). The patient received mechanical ventilation throughout the entire period of metabolic investigation. The arterial blood pH was 7.17 at the time DCA was begun. Serum sodium was 150, potassium 4.5, chloride 108, and bicarbonate 10 meq/L. The serum was negative for ketones by the nitroprusside reaction. During therapy with DCA, the pH remained between 7.2 and 7.3, despite an increase in the bicarbonate concentration of the dialysate and 200 meq additional bicarbonate. Despite the addition of an intravenous norepinephrine infusion (4–12 μg/min), he died 7½ h after DCA treatment was begun.

Case 3. The patient was a 63-yr-old white man with poorly differentiated lymphoma and associated leukemia. He had low-grade fevers and blood cultures that were positive for both gram-positive and gram-negative organisms from an unknown source for several days. Despite intensive antibiotic therapy, he rapidly developed a severe metabolic acidosis. His respiratory rate was 40/min, arterial blood pH 7.17, serum sodium 134, potassium 5.6, chloride 104, and bicarbonate 12 meq/L. Mechanical ventilation was begun, and it continued until his death. Despite the administration of bicarbonate, the pH dropped to 6.97, the serum bicarbonate decreased to 2 meq/L, and he became hypotensive. DCA therapy was begun, but the pH remained between 6.85 and 7.08 despite the administration of an additional 400 meq bicarbonate. Autopsy revealed a widely disseminated lymphoma and a necrotic abscess in a lymphomatous thyroid gland.

Case 4. The patient was a 58-yr-old white man with Hodgkin's disease, gram-negative septicemia from a urinary tract infection, and pneumonia. He developed sudden tachypnea with fever and chills and his blood pressure decreased to 80/50, for which an intravenous infusion of dopamine (200–1000 μg/min) was begun. Serum sodium was 136, potassium 4.5, chloride 108, and CO_2 11 meq/L; arterial pO_2 was 82, pCO_2 44, pH 7.08. He remained hypotensive and acidotic, despite dopamine, antibiotics, and about 100 meq of sodium bicarbonate per hour. A single infusion of DCA was administered but the patient refused mechanical ventilation. He died of respiratory failure 3 h later.

Metabolic Effects of DCA Treatment

The metabolic effects of DCA administration in patients 1–3 are shown in Figure 2. All three patients had markedly elevated initial blood lactate levels, ranging from 11.2 mM in patient no. 1 to 31 mM in patient no. 3. DCA treatment in patient no. 1 was associated with a decrease of lactate, pyruvate, and alanine levels to normal within 16 h. In contrast, patients nos. 2 and 3 experienced only transient decreases in lactate and pyruvate concentrations after each DCA infusion. Transient decreases in blood alanine concentration were noted in patient no. 2 after each DCA infusion; alanine levels continued to rise in patient no. 3 despite DCA administration. In patient no. 4, the initial blood lactate concentration was 17.1 mM, which decreased to 15.8 mM 2 h after DCA administration; pyruvate levels decreased from 0.46 to 0.24 mM during the same time, and alanine levels remained unchanged.

In patient no. 1, the blood glucose concentrations remained between 108 and 145 mg/dl during DCA treatment, while blood glycerol levels decreased from 0.21 mM before treatment to 0.09 mM 16 h later. Blood total ketone body concentrations (3-hydroxybutyrate plus acetoacetate) decreased slowly from 0.36 mM before DCA treatment to 0.04 mM 16 h later.

In patient no. 2, plasma glucose levels remained between 319 and 363 mg/dl during DCA treatment, and arterial blood pH remained between 7.2 and 7.3. The 3-hydroxybutyrate level (normal 0.26 ± 0.17 mM, mean ± SD) remained between 0.10 and 0.17 mM during treatment, and the acetoacetate level (normal 0.08 ± 0.04 mM) remained between 0.06 and 0.13 mM.

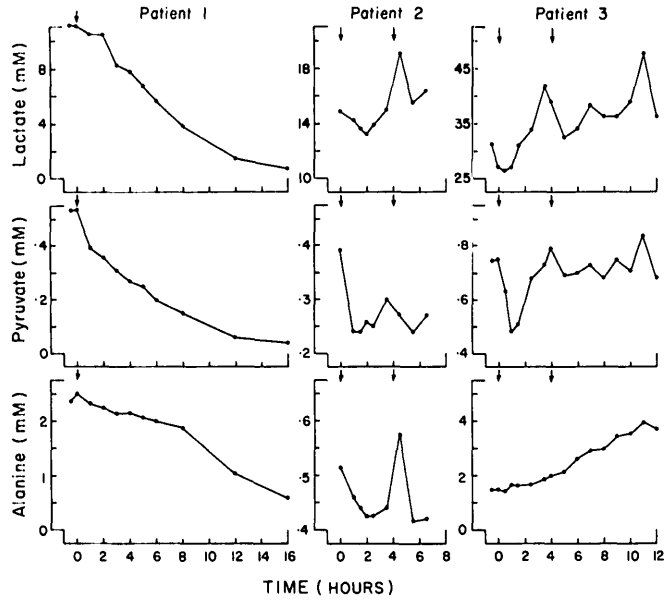

FIG. 2. Response of whole blood lactate, pyruvate, and alanine concentrations to one or two 30-min infusions of DCA (50 mg/kg body wt). Normal values (mean ± SD) from our laboratory after an overnight fast are (N = 26): lactate, 0.52 ± 0.09 mM; pyruvate, 0.04 ± 0.01 mM; alanine 0.24 ± 0.04 mM. DCA infusions are indicated by arrows.

In patient no. 3, total ketone body levels rose during treatment, from 0.52 to 1.52 mM 7 h after DCA was started, and then decreased slowly. The blood glycerol concentration remained between 0.36 and 0.55 mM during the study, and the plasma glucose concentration remained between 98 and 168 mg/dl.

In patient no. 4, total blood ketone body, glucose, and glycerol concentrations were unaffected by DCA treatment.

DISCUSSION

Several conclusions emerge from our experience with DCA in the treatment of four patients with severe lactic acidosis. In one patient, the use of DCA was associated temporally with complete amelioration of hyperlactatemia, metabolic acidosis, and shock. In the absence of measured lactate levels for many hours before treatment and other appropriate controls, we cannot be sure that DCA caused this beneficial effect. However, the rapid decrease in blood pyruvate levels in this patient immediately after DCA administration suggests that the compound was activating pyruvate dehydrogenase as expected, and may have contributed to the clinical response. In the other three patients, DCA did not ameliorate the metabolic acidosis or significantly prolong the patients' lives. However, its use was associated with transient decreases in the blood pyruvate and lactate concentrations after each infusion of DCA.

These patients were in a particularly high risk group. In a study of 52 patients with shock of various etiologies, the mortality rate was zero in the patients with blood lactate levels below 1.4 mM, and 100% in patients with lactate concentrations above 13.3 mM.[16] In a study of patients with shock due to sepsis alone, the mortality rate was 100% in patients with blood lactate levels greater than 3 mM.[17] Similarly, the mortality rate was 91% in 11 patients with septic shock with high central venous pressures whose lactates exceeded 10 mM, and 100% in seven septic patients with low central venous pressures and lactate levels above 5.3 mM.[18] Based on these data, all four of our patients fell into a group with an expected mortality rate of 90–100% with conventional therapy.

One possible explanation for the transient nature and for the small magnitude of biochemical changes in patients nos. 2, 3, and 4 is that the dose of DCA was inadequate. We based our initial dosage schedule (50 mg/kg body wt, repeated once in 4 h) on animal studies and on studies in humans with various salts of dichloroacetic acid administered orally.[19,20] Since our study began, additional data on the intravenous use of DCA in man have appeared. In one study, a 30-min intravenous infusion of DCA (50 mg/kg body wt) to six normal subjects resulted in a threefold decrease in blood lactate levels and a twofold decrease in alanine concentrations.[21] In a more recent investigation, the intravenous administration of up to 50 mg/kg body wt over 30 min in six normal subjects produced marked and prompt decreases in blood lactate and alanine concentrations.[22] Thus, in the doses we used, DCA caused sustained decreases in

blood lactate, pyruvate, and alanine levels in normal human subjects. The clearance of DCA from the circulation is presumably decreased in hypotensive subjects with poor renal perfusion, suggesting the possibility that even higher blood DCA levels are attained in these patients after DCA administration than in normal subjects.

Our observations suggest that certain side effects of DCA noted in animal and human studies are not serious enough to prevent further trials in patients with life-threatening lactic acidosis. The hypoglycemia and hyperketonemia noted in several animal and human studies were not problems in our patients. A peculiar neuropathy was recently described in animals and in a single patient treated chronically with oral DCA;[23] this has not been noted in animals treated briefly with DCA intravenously, and probably should not limit therapeutic trials of DCA in patients with severe lactic acidosis.

To date, DCA has been used to treat five patients with severe lactic acidosis, our four patients, and one reported by Irsigler and colleagues.[24] Four or five patients died shortly after DCA administration, although mild and transient biochemical improvement occurred in all. Our single surviving patient had the least severe lactic acidosis of the five. Since the use of DCA was associated with improvement in this patient, and since it has been effective in animal models of lactic acidosis, it may yet prove to be of value in the treatment of this often fatal disorder in man, perhaps in patients with marked but not extreme elevations of blood lactate levels. Clearly, controlled trials of its use in lactic acidosis of various etiologies will be necessary to determine its ultimate usefulness.

ACKNOWLEDGMENTS: We thank our many colleagues who allowed us to take part in the care of their patients. We are grateful to the nurses of the Baker 6 and Bigelow 8 Intensive Care Units for their help. Finally, we are indebted to Suzanne Bagshaw for her technical help and to Carol Bovest and Martha Chambers for typing the manuscript.

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