A CONTROLLED CLINICAL TRIAL OF DICHLOROACETATE FOR TREATMENT OF LACTIC ACIDOSIS IN ADULTS

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Abstract *Background.* Mortality is very high in lactic acidosis, and there is no satisfactory treatment other than treatment of the underlying cause. Uncontrolled studies have suggested that dichloroacetate, which stimulates the oxidation of lactate to acetyl-coenzyme A and carbon dioxide, might reduce morbidity and improve survival among patients with this condition.

Methods. We conducted a placebo-controlled, randomized trial of intravenous sodium dichloroacetate therapy in 252 patients with lactic acidosis; 126 were assigned to receive dichloroacetate and 126 to receive placebo. The entry criteria included an arterial-blood lactate concentration of ≥5.0 mmol per liter and either an arterial-blood pH of ≤7.35 or a base deficit of ≥6 mmol per liter. The mean (±SD) arterial-blood lactate concentrations before treatment were 11.6±7.0 mmol per liter in the dichloroacetate-treated patients and 10.4±5.5 mmol per liter in the placebo group, and the mean initial arterial-blood pH values were 7.24±0.12 and 7.24±0.13, respectively. Eighty-six percent of the patients required mechanical ventilation, and 74 percent required pressor agents, inotropic drugs, or both because of hypotension.

Results. The arterial-blood lactate concentration decreased 20 percent or more in 83 (66 percent) of the 126 patients who received dichloroacetate and 45 (36 percent) of the 126 patients who received placebo ($P = 0.001$). The arterial-blood pH also increased more in the dichloroacetate-treated patients ($P = 0.005$). The absolute magnitude of the differences was small, however, and they were not associated with improvement in hemodynamics or survival. Only 12 percent of the dichloroacetate-treated patients and 17 percent of the placebo patients survived to be discharged from the hospital.

Conclusions. Dichloroacetate treatment of patients with severe lactic acidosis results in statistically significant but clinically unimportant changes in arterial-blood lactate concentrations and pH and fails to alter either hemodynamics or survival. (N Engl J Med 1992;327:1564-9.)

LACTIC acidosis is a common disorder of acid–base metabolism that occurs in patients with many life-threatening illnesses. The mortality rate among patients with lactic acidosis is high,[1-3] but whether lactic acidosis influences the prognosis independently of the underlying disease and, if so, whether specific treatment and amelioration of lactic acidosis improve survival are not known.

Several uncontrolled studies have suggested that treatment with dichloroacetate may reduce not only morbidity but also mortality in patients with lactic acidosis caused by hypotension or sepsis.[4-6] Dichloroacetate ameliorates lactic acidosis by increasing myocardial glucose oxidation and contractility and by inhibiting glycolysis, thereby decreasing lactate production, as well as by increasing lactate oxidation in peripheral tissues.[7] The last effect is mediated by stimulation of pyruvate dehydrogenase, the mitochondrial enzyme that catalyzes the conversion of pyruvate (and lactate) to acetyl-coenzyme A and carbon dioxide. Thus, therapy with dichloroacetate might improve acid–base status and hemodynamics in such patients long enough to increase the chance of successfully treating the underlying cause of the lactic acidosis, thereby increasing survival.

We conducted this multicenter, placebo-controlled study to test the hypothesis that treatment with dichloroacetate significantly decreases morbidity and mortality among adult patients with severe lactic acidosis.

METHODS

The study was approved by the institutional review board of each participating hospital and was conducted under an investigational-new-drug license issued by the Food and Drug Administration. Each patient, or the closest relative if the patient was incapacitated, gave written informed consent.

The subjects were adults 18 years old or older who had been admitted to critical care units. They were enrolled in the study if they had an arterial-blood lactate concentration of ≥5.0 mmol per liter and either an arterial-blood pH of ≤7.35 or a base deficit of ≥6.0 mmol per liter. The pH value 7.35, rather than a lower one, was chosen because of the dependence of arterial pH on the patient's intrinsic respiratory rate (or ventilator setting, if he or she is receiving mechanical ventilation) and because lactic acidosis may

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coexist with illnesses (such as sepsis or liver failure) that may predispose the patient to alkalemia.[1-3] Patients were excluded if they were pregnant; if they had any of the following: a history of ketosis-prone diabetes mellitus, higher-than-moderate serum ketone levels on dipstick testing (Ames), acute ethanol intoxication, evidence of brain death on two consecutive electroencephalographic tracings, or an elevated arterial-blood lactate concentration or elevated blood gas values determined during or within one hour after a respiratory or cardiopulmonary arrest or during or within four hours after a generalized seizure; or if a decision had previously been made that the patient should not be resuscitated in case of a respiratory or cardiopulmonary arrest. No other restrictions were made regarding the underlying cause of lactic acidosis. Patients who had received therapy with sodium bicarbonate were not excluded. All patients received appropriate therapy for their underlying disease, as determined by physicians outside the study.

Sodium dichloroacetate, in the form of a 10 percent (wt/vol) solution in 0.9 percent sodium chloride, or a 0.9 percent sodium chloride placebo was prepared in sterile, pyrogen-free 30-ml glass vials with rubber stoppers. The pH of both solutions was approximately 5.0. Coded lots of vials containing drug or placebo were distributed to each participating center and stored at 4°C in the hospital pharmacy until use. Unopened vials were returned periodically to the preparation facility for reassessment of sterility, pyrogenicity, and drug concentration.

The dichloroacetate (at a dose of 50 mg per kilogram of body weight) or placebo was infused over 30 minutes into a peripheral vein; a second 30-minute infusion was begun 2 hours after the start of the first infusion.[5,6] Sixty-five percent of the patients received one or more catecholamines, other pressor drugs, or both, intermittently or continuously, during the first 12 hours after the infusions. Once treatment with dichloroacetate or placebo began, however, no sodium bicarbonate was administered as long as the arterial pH was at least 7.1, but up to 100 mmol of sodium bicarbonate was given by slow intravenous infusion each hour for up to four hours if the arterial pH was less than 7.1. No further doses of sodium bicarbonate were given, regardless of the arterial pH. Sodium bicarbonate was not given, regardless of the arterial pH, if the patient's serum sodium concentration exceeded 150 mmol per liter or if the serum osmolality exceeded 310 mOsm per kilogram.

Patients were retreated if the arterial-blood lactate concentration decreased to a value at least 20 percent below the pretreatment value within 6 hours but was $\geq$5.0 mmol per liter 12 hours after the beginning of therapy. Patients could be retreated an unlimited number of times on the basis of these criteria as long as there was no obvious drug toxicity. This protocol was based on our previous observations[5,6] that the patients who responded to dichloroacetate therapy with decreases in the arterial-blood lactate concentration to less than 5.0 mmol per liter usually did so within 6 hours and always within 12 hours after treatment began, at which time the plasma concentration of dichloroacetate was usually less than 50 μg per milliliter.

Vital signs were measured and routine tests of renal, hepatic, and hematopoietic function were performed throughout each patient's stay in the critical care unit. Changes in neurologic status were recorded with use of the Glasgow coma score.[8] The Acute Physiology and Chronic Health Evaluation (APACHE) II system[9] was used as a global measure of clinical status and prognosis. Surviving patients were followed for six months.

Clinical and Chemical Analyses

Blood was obtained from indwelling arterial catheters for immediate measurement of lactate with a YSI Lactate Analyzer or by standard American Chemical Society automated techniques. Plasma dichloroacetate concentrations were determined by published methods.[10,11] The base deficit was calculated[12] according to the following equation: 37 (exponent $\{(pH - 7.4 + 0.345y)/(0.55 - 0.09y)\} - 1$), where y = ln(partial pressure of carbon dioxide/40). Arterial systolic and diastolic blood pressures were recorded from an indwelling catheter every 15 minutes during the first 2 hours after the initiation of treatment and at least hourly thereafter. Cardiac output was estimated immediately before treatment, 30 and 60 minutes after treatment began, and at least every 4 hours thereafter for 24 hours by the thermodilution technique, with Swan–Ganz catheters.[13]

Autopsy Studies

Specimens of kidney, liver, thyroid, and heart were obtained at autopsy and were fixed in an unbuffered 37 percent formaldehyde solution saturated with calcium oxalate for examination for oxalate crystals, since oxalate is a metabolite of dichloroacetate and a potential toxin.[7] The deposition of oxalate crystals in tissues was evaluated by light microscopy and scored on a scale ranging from 0 (no crystals seen) to 3 (marked deposition of crystals).

Statistical Analysis

Sample-size estimates were calculated before the start of the study for mortality only, since it was assumed that the sample size needed to detect a difference in mortality would be larger than that needed to detect a difference in morbidity. We also assumed that mortality would be distributed exponentially, that patients would be followed for a minimum of 30 days, that 10 percent of the patients would be lost to follow-up, and that a P value of 0.05 in a one-sided test would be used to determine statistical significance.[14,15] A sample of 240 patients was estimated to be necessary. If the survival rate at 24 hours was 40 percent in the placebo group and 55 percent in the dichloroacetate group, then a study with a sample of this size would have a 90 percent chance of detecting a difference of this magnitude between the two groups. Separate randomization sequences were prepared for each clinical center by the Data Coordinating Center, with use of the urn design.[16]

The statistical analyses were performed with SAS software.[17] The chi-square test was used to compare categorical variables in the two groups and Student's t-test to compare quantitative variables.[18] Analysis of covariance was used to adjust for pretreatment values in comparisons of the changes in arterial-blood lactate concentrations and other quantitative measures.[19] The length of time to discharge or death was measured from the time of the initiation of dichloroacetate therapy. Survival curves were calculated by the Kaplan–Meier method,[20] with data stratified according to treatment group, and compared with the log-rank test.[21] Logistic-regression analysis was used to assess the relation between mortality (during a fixed period) and treatment, with control for other possible risk factors.[22] All reported P values are two-sided.

Results

Recruitment and Demographic Characteristics of the Patients

We screened 810 potentially eligible patients at the 10 centers during the study period. Of these, 255 (31 percent) entered the study; 128 were assigned to receive dichloroacetate and 127 to receive placebo. Three patients (two in the dichloroacetate group and one in the placebo group) were excluded from the analysis because their base-line arterial-blood lactate concentrations were less than 5.0 mmol per liter.

The characteristics of the two treatment groups were similar at base line (Table 1), except that a significantly larger number of patients in the dichloroacetate group had hemorrhagic shock (P = 0.027) or were receiving mechanical ventilation (P = 0.045) than in the placebo group. In addition, the patients in the dichloroacetate group tended to have lower systolic blood pressures and higher arterial-blood lactate concentrations, serum glucose concentrations, and

APACHE II scores. Circulatory shock due to hemorrhage, myocardial failure, or sepsis was identified on the basis of established criteria[23-27] and was the most common coexisting illness. Most patients, however, had insufficiency or failure of multiple organ systems.

Morbidity

A response to treatment was defined as a decrease of 20 percent or more in the arterial-blood lactate concentration from the pretreatment value. Eighty-three patients (66 percent) in the dichloroacetate group had a response to treatment, as compared with 45 patients (36 percent) in the placebo group (P = 0.001). Fifteen patients in the dichloroacetate group and five in the placebo group were retreated approximately 12 hours after the first treatment; seven of those in the dichloroacetate group and none of those in the placebo group responded to the second treatment. One patient in the dichloroacetate group received a third treatment and responded to that treatment.

The decrease in the mean arterial-blood lactate concentration was significantly greater in the dichloroacetate group than in the placebo group beginning one hour after treatment (P<0.001) (Fig. 1). The magnitude of this difference was small, however, ranging from about 1 to 3 mmol per liter. Furthermore, although dichloroacetate therapy was associated with a significant increase in pH (P = 0.005 at two, three, and four hours) and a significant decrease in the base deficit (P = 0.007 at two, three, four, and six hours; data not shown), the absolute effect on pH at six hours (0.03 units, P = 0.07) was also very small. There were no significant differences in serum bicarbonate concentrations or anion-gap values between the groups during the first six hours of treatment. Neither systolic blood pressure nor cardiac output differed significantly between the dichloroacetate group and the placebo group at any time during the study.

Table 1. Clinical Characteristics of 252 Patients with Lactic Acidosis.*

Index	Dichloroacetate (N = 126)	Placebo (N = 126)
Age (yr)	56±18	56±17
Male sex (%)	60	53
Arterial-blood lactate (mmol/liter) (normal, 0.5–1.0)	11.6±7.0	10.4±5.5
Arterial-blood pH	7.24±0.12	7.24±0.13
Base deficit (mmol/liter)	13.2±5.5	14.1±5.4
$PaCO_2$ (mm Hg)	29.8±9.6	27.9±10.9
Serum bicarbonate (mmol/liter) (normal, 21–27)	13.6±5.1	12.7±4.7
Systolic blood pressure (mm Hg)	97±27	103±29
Systolic blood pressure <90 mm Hg (%)	41	32
Glasgow coma score (normal, 15; range, 3–15)	7.4±4.6	7.9±4.9
APACHE II score (normal, 0; range, 1–42)	21.0±8.3	19.2±8.1
Septic shock (%)	56	59
Cardiogenic shock (%)	16	18
Hemorrhagic shock (%)†	30	18
Failure of more than four systems (%)‡	54	48
Pressor or inotropic drug therapy (%)	78	71
Mechanical ventilation (%)§	90	82
Serum glucose (mg/dl)¶ (normal, 65–110)	234±170	196±130
Serum creatinine (mg/dl)‖ (normal, 0.7–1.4)	2.9±1.7	3.2±2.7

*Plus–minus values are means ±SD. $PaCO_2$ denotes partial pressure of arterial carbon dioxide.

†P = 0.027 for the comparison between the groups.

‡Includes neurologic, respiratory, gastrointestinal, renal, metabolic, and hematologic insufficiency or failure.

§P = 0.045 for the comparison between the groups.

¶To convert values to millimoles per liter, multiply by 0.056.

‖To convert values to millimoles per liter, multiply by 88.4.

Lactic acidosis was considered to have resolved if the arterial-blood lactate concentration fell below 5.0 mmol per liter and either the arterial pH rose above 7.35 or, for patients whose pretreatment pH values were greater than 7.35, the base deficit became less than 6 mmol per liter. In 36 of the 55 patients (65 percent) in the dichloroacetate group and 19 of the 52 patients (37 percent) in the placebo group whose base-line arterial-blood lactate concentrations were between 5.0 and 8.9 mmol per liter (the median base-line concentration), lactic acidosis resolved (P = 0.002). In contrast, there was no significant difference in the rate of resolution of acidosis (23 percent vs. 25 percent, P = 0.84) between the groups among patients whose pretreatment arterial-blood lactate concentrations were greater than 8.9 mmol per liter. Thus, the percentage of patients in the dichloroacetate group who had resolution of lactic acidosis decreased as the lactate concentration increased.

Mortality

The survival rates in the two treatment groups were not significantly different (P = 0.18 by the log-rank test) (Table 2). The median survival was 29 hours in the dichloroacetate group and 38 hours in the placebo group. Only 12 percent of the dichloroacetate group and 17 percent of the placebo group lived to be discharged from the hospital.

The survival rates at 24 hours were 54 percent in the dichloroacetate group and 59 percent in the placebo group. The results of logistic-regression analysis indicated that survival for 24 hours was significantly related to the arterial-blood lactate concentration (P = 0.02), pH (P<0.001), systolic blood pressure (P<0.001), APACHE II score (P<0.001), and the presence or absence of cardiogenic shock (P = 0.04) or hemorrhagic shock (P = 0.03), but not to treatment with dichloroacetate.

Because dichloroacetate had previously been shown to increase cardiac output and blood pressure in patients with lactic acidosis and hypotension,[5] we also compared survival rates among subgroups of patients with or without hypotension. The rates of survival at 72 hours for patients with pretreatment

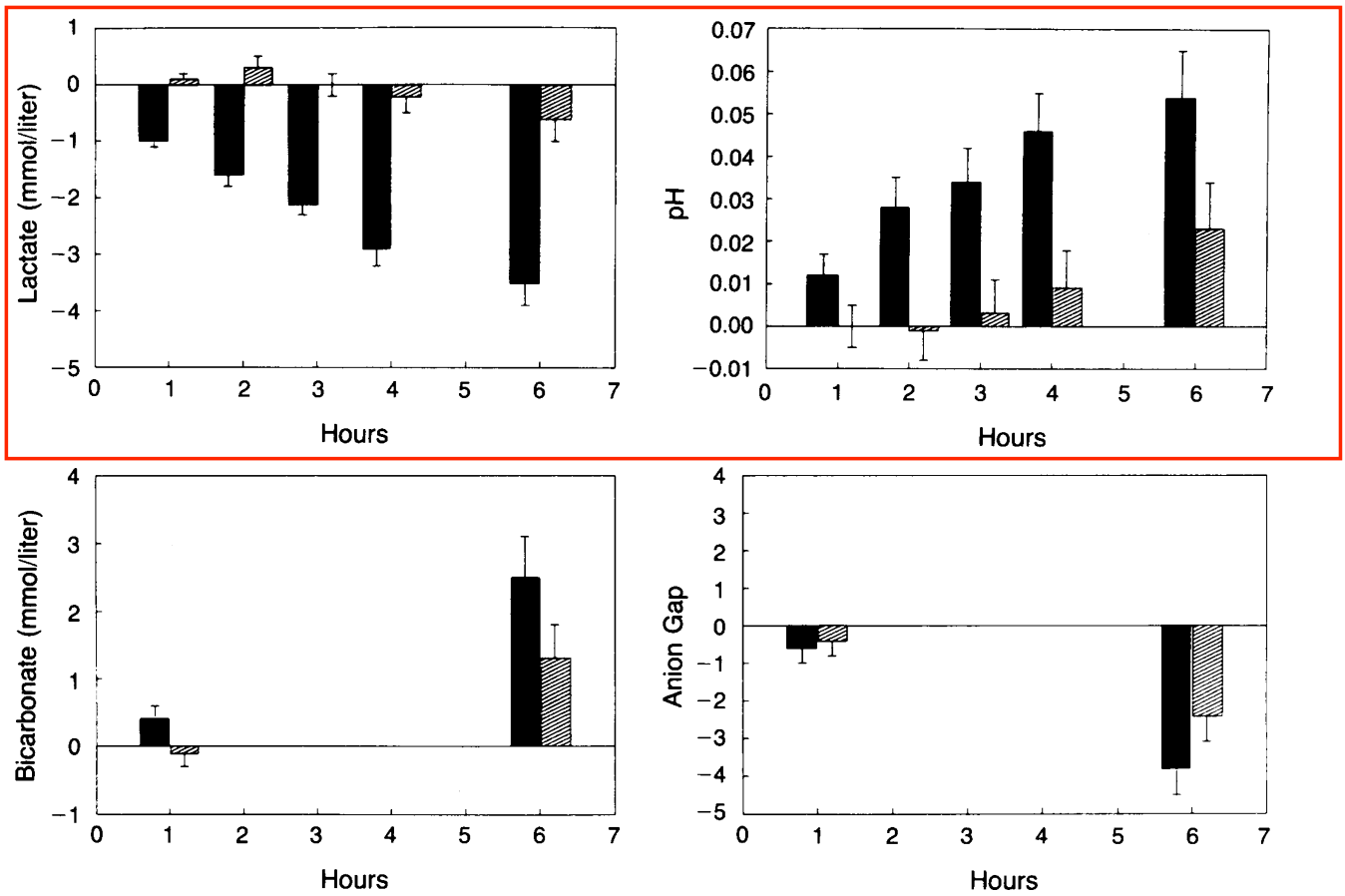

Figure 1. Changes in the Mean (±SE) Arterial-Blood Lactate Concentration, Arterial-Blood pH, Serum Bicarbonate Concentration, and Serum Anion Gap in Patients with Lactic Acidosis during the Six Hours after the First Treatment with Dichloroacetate (Solid Bars) or Placebo (Hatched Bars).

After treatment, the decrease in the arterial-blood lactate concentration was significantly greater at all times ($P<0.001$) and the increase in the arterial-blood pH was significantly greater at two, three, and four hours ($P = 0.005$) among the patients who received dichloroacetate as compared with those who received placebo. The serum bicarbonate concentrations and anion-gap values were not significantly different in the two groups. The numbers of patients studied were as follows: 236 at one hour, 224 at two hours, 216 at three hours, 208 at four hours, and 189 at six hours.

systolic blood pressures of ≤90 mm Hg were 14 percent for the dichloroacetate group and 12 percent for the placebo group, whereas those for patients with pretreatment systolic blood pressures of >90 mm Hg were 47 percent and 55 percent, respectively ($P = 0.43$) (Fig. 2).

More patients who received dichloroacetate died in the first six hours after the initiation of treatment (24 percent vs. 17 percent), but the difference was not significant (Table 3). Among the 201 patients who survived for more than six hours, however, lactic acidosis resolved in 58 percent of those treated with dichloroacetate (56 of 96 patients), as compared with 43 percent of those treated with placebo (45 of 105 patients; $P = 0.03$).

Monitoring and Safety of Treatment

There were no instances in which the treatment code was broken or the patients or care givers became aware of the treatment. All patients randomly assigned to receive dichloroacetate had measurable plasma concentrations of this agent. The mean (±SD) peak plasma dichloroacetate concentration was 146±99 μg per milliliter after the first dose and 182±95 μg per milliliter after the second dose. The mean plasma half-life for dichloroacetate was 2.6±2.3

Table 2. Survival of Patients with Lactic Acidosis, According to Treatment Group.*

Length of Survival	Dichloroacetate (N = 126)	Placebo (N = 126)
	no. (%)	
More than 24 hr	68 (54)	74 (59)
More than 72 hr	42 (33)	52 (41)
More than 30 days	17 (13)	22 (17)
More than 6 mo	10 (8)	11 (9)
To transfer from critical care unit	21 (17)	26 (21)
To discharge from hospital	15 (12)	21 (17)

*P>0.05 for all comparisons between the groups.

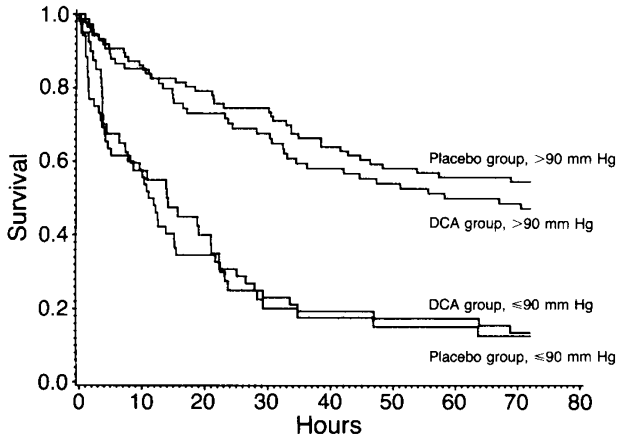

Figure 2. Kaplan–Meier Survival Curves for the 72 Hours after the First Treatment with Dichloroacetate (DCA) or Placebo in Patients with Pretreatment Systolic Blood Pressures ≤90 mm Hg and Patients with Pretreatment Systolic Blood Pressures >90 mm Hg.

The differences between the dichloroacetate group and the placebo group were not significant in either subgroup or for the subgroups combined.

hours after the first dose and 7.0±4.4 hours after the second.

Continuous electrocardiographic monitoring of the patients disclosed no evidence of rhythm disturbances related to the administration of either agent. Six hours after treatment began, the mean partial pressure of arterial carbon dioxide was significantly higher in the dichloroacetate group than in the placebo group (31 vs. 28 mm Hg, P = 0.02), whereas the values for oxygen tension (104 vs. 110 mm Hg) were not significantly different (P = 0.32). At 12 hours, the patients who received dichloroacetate had lower values for partial pressure of arterial oxygen (101 vs. 115 mm Hg, P = 0.03), higher values for partial pressure of arterial carbon dioxide (31 vs. 29 mm Hg, P = 0.07), and lower anion-gap values (16 vs. 18 mmol per liter, P = 0.05).

Specimens of various tissues obtained at autopsy from 22 of the 113 patients in the dichloroacetate group who died (19 percent) and 22 of the 110 patients in the placebo group who died (20 percent) were examined for oxalate crystals. The mean (±SE) oxalate-crystal scores for the dichloroacetate and placebo groups were 0.7±0.1 and 0.3±0.1, respectively, for the kidney (P = 0.01), but they were not significantly different for the heart, thyroid, or liver. In tissue from three patients in the dichloroacetate group but none in the placebo group at least one kidney section was scored 2. These three patients did not have high plasma dichloroacetate concentrations. In the case of one of the three patients, the presence of oxalate crystals was believed to have been due to a chronic process unrelated to dichloroacetate therapy.

Table 3. Survival According to Treatment Group and Resolution of Lactic Acidosis.*

Subgroup	Dichloroacetate (N = 126)	Placebo (N = 126)
	no. (%)	
Died within 6 hr	30 (24)	21 (17)
Died within 7–72 hr		
No resolution of acidosis	37 (29)	49 (39)
Resolution of acidosis	17 (13)	4 (3)
Survived >72 hr		
No resolution of acidosis	3 (2)	11 (9)
Resolution of acidosis	39 (31)	41 (33)

*Resolution of lactic acidosis was defined as a decrease in the arterial-blood lactate concentration to less than 5 mmol per liter and an increase in the arterial-blood pH to more than 7.35. For patients whose pretreatment arterial-blood pH was greater than 7.35, a decrease in the base deficit to less than 6 mmol per liter was substituted as a criterion.

Discussion

Lactic acidosis has most often been defined as a metabolic acidosis in which the arterial-blood lactate concentration equals or exceeds 5 mmol per liter.[1-3] Although hyperlactatemia is frequently associated with acidemia, clinical factors, such as the ventilatory status of the patient or the presence of sepsis or liver failure, may mitigate against the expected decline in pH.[2] The presence of hyperlactatemia is associated with a high mortality rate, particularly among patients with hypotension.[1-3] Most of our patients had some type of circulatory shock, and many remained hypotensive (systolic blood pressure, <90 mm Hg) despite treatment with inotropic or pressor drugs.

The rationale for this controlled clinical trial of dichloroacetate therapy in patients with lactic acidosis was based on its lactate-lowering effect in animals[7] and the results of open clinical studies[4-6] in which the drug significantly improved acid–base status and appeared to prolong survival in some patients. In virtually all tissues, dichloroacetate is a potent activator of pyruvate dehydrogenase, and it inhibits glycolysis in skeletal muscle.[7] Dichloroacetate may also improve myocardial glucose and lactate oxidation and left ventricular function in patients with conditions, such as sepsis or myocardial failure or ischemia, that impair perfusion and oxygenation of peripheral tissues and increase the hypoxic stimulus for lactic acid formation.[7,28-30]

We found that dichloroacetate, as predicted, was superior to placebo in reducing hyperlactatemia and improving acid–base status. The absolute magnitude of these changes was small, however, and dichloroacetate therapy did not increase blood pressure or decrease mortality.

For many years it has been assumed that elevated intracellular or circulating concentrations of lactate or hydrogen ions, or both, diminish myocardial contractility and reduce the responsiveness of myocardial cells to catecholamines.[1-3] Implicit in this assumption is the theory that the depressed myocardial contractility seen in lactic acidosis might be reversed if the lactate and hydrogen ion concentrations were lowered.

Our findings suggest that lactic acidosis may be a marker of advanced functional cardiac deterioration but not necessarily its cause. Moreover, despite suggestions to the contrary,[31-34] we think that lactic acidosis does not necessarily reflect poor oxygen delivery to the tissues, since the metabolic acidosis can be ameliorated in some patients without changing cardiac output or survival. One interpretation of our results, therefore, is that an arterial-blood lactate concentration above 5.0 mmol per liter and a pH below 7.35 are epiphenomena of limited pathophysiologic importance in patients who are already severely ill and that overall survival may be largely independent of further changes in acid–base status.

Might the initiation of dichloroacetate therapy earlier in the course of the illness improve outcome in patients like those we studied? The clinical course of patients with less severe hyperlactatemia (for example, those with arterial-blood lactate concentrations below 5.0 mmol per liter) is unknown. Once lactic acidosis is established, however, it is clear that the patient's prognosis is poor and is probably not influenced by treatment of hyperlactatemia. Recognition and treatment of the underlying causes of lactic acidosis remain the only realistic hope for improving survival among patients with this condition.

We are indebted to the house staff, nurses, and attending physicians of the critical care units where this research was conducted for their help in identifying and recruiting patients and to Mrs. Penny Moeller, Mrs. Sheri Crouch, and Mrs. Melody Riedy for administrative assistance.

Appendix

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