Controlled Clinical Trial of Dichloroacetate for Treatment of Congenital Lactic Acidosis in Children

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ABSTRACT

OBJECTIVE. Open-label studies indicate that oral dichloroacetate (DCA) may be effective in treating patients with congenital lactic acidosis. We tested this hypothesis by conducting the first double-blind, randomized, control trial of DCA in this disease.

METHODS. Forty-three patients who ranged in age from 0.9 to 19 years were enrolled. All patients had persistent or intermittent hyperlactatemia, and most had severe psychomotor delay. Eleven patients had pyruvate dehydrogenase deficiency, 25 patients had 1 or more defects in enzymes of the respiratory chain, and 7 patients had a mutation in mitochondrial DNA. Patients were preconditioned on placebo for 6 months and then were randomly assigned to receive an additional 6 months of placebo or DCA, at a dose of 12.5 mg/kg every 12 hours. The primary outcome results were (1) a Global Assessment of Treatment Efficacy, which incorporated tests of neuromuscular and behavioral function and quality of life; (2) linear growth; (3) blood lactate concentration in the fasted state and after a carbohydrate meal; (4) frequency and severity of intercurrent illnesses and hospitalizations; and (5) safety, including tests of liver and peripheral nerve function.

OUTCOME. There were no significant differences in Global Assessment of Treatment Efficacy scores, linear growth, or the frequency or severity of intercurrent illnesses. DCA significantly decreased the rise in blood lactate caused by carbohydrate feeding. Chronic DCA administration was associated with a fall in plasma clearance of the drug and with a rise in the urinary excretion of the tyrosine catabolite maleylacetone and the heme precursor δ-aminolevulinate.

CONCLUSIONS. In this highly heterogeneous population of children with congenital lactic acidosis, oral DCA for 6 months was well tolerated and blunted the postprandial increase in circulating lactate. However, it did not improve neurologic or other measures of clinical outcome.
The term “congenital lactic acidosis” includes a number of inborn errors of mitochondrial metabolism in which the efficient conversion of substrate fuels into adenosine triphosphate is perturbed. Most biochemically proven causes of congenital lactic acidosis are attributed to loss-of-function mutations in genes that encode the pyruvate dehydrogenase complex (PDC), especially the X chromosome–linked E1α subunit of pyruvate dehydrogenase or 1 or more of the 5 complexes of the respiratory chain.1,2 Other causes of congenital lactic acidosis include point mutations and deletions in mitochondrial DNA (mtDNA) that give rise to discrete clinical syndromes such as mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS); myoclonus, epilepsy, ragged red fibers; and characteristic mtDNA deletion syndromes.3,4

The biochemical hallmark of congenital lactic acidosis is the abnormal accumulation of lactate in body fluids and tissues, although many patients with deficiencies in PDC or respiratory chain enzymes maintain normal or near-normal concentrations of lactate in blood and cerebrospinal fluid (CSF). The clinical presentation and course of congenital lactic acidosis is extremely diverse, even among patients with identical enzymatic or genetic defects. However, highly oxidative tissues, such as the nervous system, skeletal muscle, heart, and kidney cortex, are particularly vulnerable to inhibition of aerobic carbohydrate metabolism. Consequently, the most common clinical manifestations of congenital lactic acidosis include neurologic and neuromuscular degeneration, peripheral neuropathy, cardiomyopathy, cardiac conduction disturbances, and renal dysfunction. Early death usually ensues from progressive organ system failure or from acute exacerbation of the underlying acid-base disorder or both. Treatment options for congenital lactic acidosis generally have been disappointing.2,5 Various diets or nutritional supplements, often used in combination, have been administered in an uncontrolled manner, making it difficult to assess their efficacy and safety.

Dichloroacetate (DCA) enters mitochondria, probably via the transporter systems for pyruvate and other monocarboxylates, and stimulates the activity of the PDC by inhibiting the phosphorylation (and inactivation) of the E1α subunit catalyzed by pyruvate dehydrogenase kinase (Fig 1).6 In some patients with E1α deficiency, DCA may also stabilize the enzyme and decrease its rate of turnover.7,8 By maintaining PDC in its active, unphosphorylated form, DCA accelerates the aerobic oxidation of glucose, pyruvate, and molecules, such as alanine and lactate, that are in equilibrium with pyruvate, to acetyl coenzyme A that enters the tricarboxylic acid (TCA) cycle. Reducing equivalents, in the forms of reduced nicotinamide adenine dinucleotide and flavin adenine dinucleotide, generated by the PDC-catalyzed step and by the dehydrogenases of the TCA cycle, donate electrons to the respiratory chain. In theory, therefore, administration of DCA should stimulate both the oxidative removal of lactate (and accompanying protons) and the synthesis of adenosine triphosphate in mitochondria that contain both residual PDC activity and a functional TCA cycle and respiratory chain. Therefore, as described previously,9 the rationale for using DCA in congenital lactic acidosis is predicated on its presumed ability to improve fuel metabolism in cells that possess both normal or residual PDC activity and a functional respiratory chain.

Open-label studies have reported that the chronic, oral administration of DCA is effective in reducing blood, CSF, or brain lactate concentrations and in improving morbidity in some patients with defects in the PDC or the respiratory chain or with mtDNA mutations.9,10 However, it also may cause hepatocellular and peripheral nerve toxicity, which are thought to be reversible after reduction in dosage or withdrawal of DCA.11,12

To gain insight into the chronic safety and efficacy of DCA for the treatment of congenital lactic acidosis, we conducted a single-center, prospective, randomized, double-blind, placebo-controlled trial in children with PDC or respiratory chain deficiencies or with mtDNA mutations that give rise to MELAS or myoclonus, epilepsy, ragged red fibers. We tested the hypotheses that chronic DCA is superior to placebo in safely and significantly reducing blood lactate concentrations, improving neurologic and neurobehavioral outcomes, increasing linear growth, and decreasing the frequency and severity of intercurrent illnesses and hospitalizations.

METHODS
The trial was conducted in the General Clinical Research Center (GCRC) at the University of Florida and was approved by the University’s Institutional Review Board.
It was performed under the auspices of an investigator-sponsored Investigational New Drug designation by the Food and Drug Administration and was funded by both federal and nonfederal grants.

The trial was managed by a Steering and Planning Committee that comprised the study chairman (P.W.S.) and vice chairman (D.S.K.), neither of whom had patient care responsibilities; 2 biostatisticians; a clinical pharmacologist–mass spectrometrist; a research dietician; a research pharmacist; and the clinical investigators. A Data Safety Monitoring Board (DSMB) included 2 experts in genetic metabolic diseases, a biostatistician, and a lay member, none of whom was affiliated with the University of Florida or Case Western Reserve University.

Participants

Diversity in the clinical expression and the course of congenital lactic acidosis, even among individuals who harbor the same gene mutation, is an irreducible characteristic of this group of diseases. Because of the rarity of individual disorders and their phenotypic heterogeneity, it was both logistically impractical and scientifically unjustifiable to restrict enrollment to a specific genotype or phenotype. Accordingly, we accepted the premise that congenital defects in PDC or respiratory chain complexes (caused by mutations in nuclear DNA or mtDNA) have in common a problem of mitochondrial energy failure, with clinical and biochemical manifestations varying more in intensity than in type among patients. Furthermore, we postulated that a uniform combination of quantitative and qualitative measures of host and organ system function could be applied to the prospective evaluation of individuals with mitochondrial energy failure, despite genotypic and clinical diversity. Finally, we assumed that successful therapeutic intervention for these disorders could be achieved at a critical site in mitochondrial intermediary metabolism, namely DCA activating the PDC.

We recruited patients worldwide and maintained awareness about the trial through a study-specific Web site and by announcements at meetings and in publications by organizations that are oriented toward rare diseases in general or mitochondrial disorders in particular. The patient population consisted of children who were aged 3 months to 18 years at the time of enrollment. Patients who were younger than 3 months were considered too young for entry for 2 practical reasons: (1) because, in our experience >3 months are often required after clinical presentation to secure definitive enzymatic or molecular diagnosis and to obtain other biochemical tests that are required to fulfill additional inclusion and exclusion criteria (below) and (2) because repeated transportation of very young infants over long distances, often in small planes, would pose undue hardship for the patient and the family.

At entry, the following additional inclusion criteria had to be met: (1) 3 basal venous lactate concentrations \( \geq 2.5 \text{ mmol/L} \) or arterial blood lactate levels \( \geq 2 \text{ mmol/L} \) or CSF lactate levels \( \geq 2.5 \text{ mmol/L} \) or any combination of these that were obtained on at least 3 occasions over at least 1 month and within 6 months before entry or an increase in blood lactate of at least 1 mmol/L over basal after a carbohydrate meal challenge; (2) enzymatic or molecular genetic proof of a defect in the PDC, 1 or more respiratory chain enzymes, or an enzyme of the TCA cycle; and (3) biochemical verification of the ability to withstand a fast for 4 hours (if 2 years or younger) or 12 hours (if older than 2 years) without developing hypoglycemia, defined as a blood glucose <50 mg/dL.

Biochemical proof of a deficiency in the PDC or of 1 or more complexes of the respiratory chain or molecular genetic evidence of a mutation in mtDNA was made by laboratories that are recognized as diagnostic referral centers for mitochondrial diseases in North America or Australia. The results of all biochemical and molecular genetic studies were reviewed by the chairman and the vice chairman of the Steering and Planning Committee and the chairman of the DSMB, and a unanimous decision had to be reached for the patient to qualify for enrollment.

A “basal” state was defined as that in which the patient had not been fed for at least 4 hours and was in a metabolically stable condition free of acute illness, such as seizures, infection, or fever. We required that venous lactates be obtained from indwelling catheters in the absence of tourniquet pressure. Basal venous blood lactate levels for healthy adults typically are 0.5 to 1.0 mmol/L \( ^{13} \) and are similar for healthy children.\(^ {14} \)

Patients with PDC deficiency often manifest normal lactate levels while maintaining so-called ketogenic diets that are high in fat but may develop marked hyperlactatemia soon after carbohydrate feeding. Therefore, we evaluated all patients with a carbohydrate “challenge” test that we used repeatedly throughout the trial. A standard 52% carbohydrate liquid meal (Ensure Plus; Ross Laboratories, Columbus, OH) was administered in the basal state in an amount equivalent to the patient’s normal energy intake for the morning feeding. Venous blood lactate levels were measured 1 and 2 hours after the meal or beyond 2 hours when clinically indicated. When there was previous clinical evidence of hyperlactatemia after carbohydrate feeding, we conducted the challenge test in 2 stages, initially using a half-strength (26%) carbohydrate meal. When a child exhibited a rise in venous lactate \( \geq 1 \text{ mmol/L} \) after this meal, no additional testing was required and the eligibility criterion was met. When the lactate rise was <1 mmol/L, the standard (52%) carbohydrate meal was administered the next day.

Concurrent therapies, such as sodium bicarbonate or other drugs, diets, vitamins, or co-factors, that were
initiated before enrollment were not changed, unless there was clinical concern about the safety or adequacy of the diets or other therapies. In other words, appropriate standard medical care was established before entry and did not alter the eligibility of prospective subjects.

Patients were excluded when they had (1) secondary forms of lactic acidosis, for example, as a result of impaired oxygenation or circulation; (2) hyperlactatemia associated with proven biotinidase deficiency (biotin-responsive congenital lactic acidosis) or with primary disorders of gluconeogenesis; (3) primary, defined organic acidurias other than lactic acidosis, for which effective therapy was available (eg, propionic aciduria); (4) primary disorders of amino acid metabolism; (5) primary disorders of fatty acid oxidation; (6) malabsorption syndromes associated with β-lactic acidosis; (7) renal insufficiency, defined as a requirement for chronic dialysis, a serum creatinine concentration ≥1.2 mg/dL, or a creatinine clearance <60 mL/min; or (8) primary hepatic disease unrelated to congenital lactic acidosis.

Study Design
This was a prospective, randomized, double-blind trial in which patients received placebo for 6 months before being randomly assigned to receive placebo or DCA treatment for an additional 6 months. Thereafter, all patients were treated with DCA for a minimum of 12 additional months, in a double-blind manner. Patients were evaluated in the GCRC at months 0, 1, and 3 and every 3 months thereafter.

Drug Treatment
Crystalline DCA was obtained from a commercial chemical supplier (TCI America, Eugene, OR), who submitted a Master File with the Food and Drug Administration regarding manufacturing details. DCA was formulated by the Shands Hospital Investigational Pharmacy Service, according to published specifications. The Pharmacy Service and a study-specific Pharmacology Core were responsible for testing final drug formulations for pyrogenicity, stability, and content. The formulation was liquid and contained thiamine/HCl (0.2% wt/vol) and DCA (5% wt/vol), both of which are bitter tasting. The taste was masked by adding an artificial sweetener, and a red coloring was added to the product to enhance patient acceptance.15 Thiamine was included because studies in rodents indicated that it mitigates the peripheral neuropathy that is induced experimentally by DCA.16 The placebo solution was formulated in an identical manner, except for the absence of DCA. Products were provided to families in 400-mL amber-colored glass bottles that were to be refrigerated at home. At each GCRC admission, unused product was returned, volume was measured as an indicator of compliance, and the patient was discharged with a new supply of DCA or placebo. The dose was 25 mg DCA/kg body weight per day, administered as 12.5 mg/kg every 12 hours. Although the trial was designed to administer DCA or placebo by mouth or feeding tube, a provision was made for parenteral administration of product when a patient was too ill to receive it by the usual route. Therefore, at each GCRC visit, families received a new set of 25-mL vials of product (10% wt/vol) that coincided with the randomization code for each patient, together with detailed instructions for use by local hospital personnel. Vials were kept refrigerated at home. On the basis of previous experience, the recommended intravenous DCA dose was 50 mg/kg, administered over 10 to 15 minutes, and repeated every 12 hours until the patient could return to the oral dose.

Metabolic Evaluation of Patients

Diet Plan
Nutritional support for each patient was individualized to maintain adequate growth and development. In many cases, clinical and biochemical evaluation had already led to restrictions in specific energy sources, such as carbohydrates or fats. The composition of the diet for each patient remained fixed after randomization, provided that no subsequent compelling clinical or biochemical evidence occurred to warrant dietary modifications. Although the long-term efficacy of specific nutritional regimens in congenital lactic acidosis has never been evaluated in a controlled trial, diet could be an important variable in influencing the course of patients who were randomly assigned in this trial. Therefore, we developed a nutrition-oriented data form that provided information about each patient’s dietary intake throughout their participation in the study. At each visit, the GCRC research dietitian interviewed the patient and the family regarding specific nutrient and energy intake and dietary compliance. Reasons for changing previous dietary instructions were explored, and the bionutritionist completed the data form and forwarded it to the Biostatistics Coordinating Center.

Lactate Monitoring
A potential concern of the study was that we provide a sufficient test of the hypothesis that DCA significantly improved the metabolic state of patients with congenital lactic acidosis, as assessed by monitoring lactate. On the basis of data from open-label and placebo-controlled trials of DCA in children and adults with acquired or congenital forms of lactic acidosis and from pharmacologic investigations in normal volunteers, we postulated that the chronic administration of DCA would reduce venous blood lactate concentrations at least 25% below baseline levels. However, it could be difficult to demonstrate a metabolic effect of DCA if this were based solely on changes from basal lactate concentrations, even in chronically ill patients. Therefore, to maximize the pros-
pects of demonstrating a metabolic benefit of DCA, we undertook the following procedures. First, repeated blood samples for lactate determinations were collected before and during DCA (or placebo) administration under standardized conditions, defined above as “basal.” Second, a provocative carbohydrate challenge test (vida supra) was undertaken before treatment (month 0) and during subsequent admissions to assess the ability of DCA to modify dietary-induced increases in blood lactate that would be expected to occur in patients with a defect in pyruvate oxidation. Blood for lactate (and glucose) was obtained from a central venous catheter or from a catheter that was placed in a peripheral vein. In the latter case, at least 15 minutes elapsed before blood was withdrawn, to minimize the effect of discomfort on blood lactate levels. Blood was obtained using minimal or no tourniquet pressure and was placed immediately into 5-mL ice-cold tubes that contained heparin and sodium fluoride; tubes were stoppered, inverted gently several times, and transferred immediately for analysis in the GCRC Core Laboratory (Glucose/Lactate Analyzer; YSI, Yellow Springs, OH).

**Lumbar Puncture**

A lumbar puncture was performed on patients on entry into the study and was repeated at 6-month intervals for examination of CSF. Aliquots were collected serially for glucose, lactate, and DCA. We recognized that parents of infants or children and the patients themselves could be reluctant to accept sequential lumbar punctures as part of participating in the trial. Therefore, the 11 patients in whom lumbar puncture was refused by them or their parents were not denied entry and randomization but were subjected to all other experimental procedures. Magnetic resonance spectroscopy was not used in this study to assess brain lactate levels but was used in another controlled trial of DCA in older patients with MELAS.17

**DCA Kinetics and Biotransformation**

We administered a single dose of 100% 1,2-[13C] DCA (Cambridge Isotopes, Cambridge, MA) or placebo by mouth to each patient at a dose of 12.5 mg/kg at the end of admission (0) and every 6 months thereafter. The [13C] product was formulated and tested in a manner of admission (0) and every 6 months thereafter. The latter case, at least 15 minutes elapsed before blood was withdrawn, to minimize the effect of discomfort on blood lactate levels. Blood was obtained using minimal or no tourniquet pressure and was placed immediately into 5-mL ice-cold tubes that contained heparin and sodium fluoride; tubes were stoppered, inverted gently several times, and transferred immediately for analysis in the GCRC Core Laboratory (Glucose/Lactate Analyzer; YSI, Yellow Springs, OH).

**Tyrosine and Heme Metabolism**

Rats and humans who are exposed to DCA have altered tyrosine and heme metabolism that may relate to the clinical toxicology of the drug.19,20 Accordingly, we collected blood and 24-hour urine samples from patients at the same times as for DCA analyses for quantification by gas chromatography–liquid chromatography–mass spectrometry of plasma or urine concentrations of tyrosine, maleylacetone, fumarylacetone, succinylacetone, fumarate, β-hydroxybutyrate, and δ-aminolevulinate.21,22 Urinary levels of creatinine also were determined by liquid chromatography–mass spectroscopy simultaneously with the above analytes.21

**Other Chemistries**

The Clinical Chemistry Laboratory of Shands Hospital performed routine tests of renal, hepatic, and hematologic function; lipid status; and urinalyses at each admission. The laboratory also measured serum thyrotropin levels every 6 months.

**Quality-of-Life Assessment**

**Clinical Examination**

A comprehensive physical and neurologic examination that included the National Institute of Mental Health standardized neurologic examination, as previously described (A. Belman, MD, and E.M.F., unpublished data) was performed during each admission.

**Neurobehavioral Evaluation**

Neurobehavioral evaluations were completed for each patient by a clinical pediatric behavioral psychologist. Because there is no 1 available test of cognitive function that spans infancy to adulthood, we elected to follow the model used in other developmental studies of infants and children neurologic impairment and designed a separate, brief battery for 2 age groups (ages 3–30 months and ages 30 months and older). We also selected the Vineland Adaptive Behavior Scale,23 a parent/caregiver interview-based measure that provides data on a child’s development across 3 broad domains of functioning (daily learning skills, communication skills, and motor skills). This allowed us to ascertain an index of development in the event that the patient was too ill to participate in the neurobehavioral assessment. For children who were older than 30 months, we also attempted to obtain brief assessments of attention, receptive language, visuo-constructional skills, and speed of repetitive finger movement.24 These tasks were included to permit possible assessment of a variety of higher brain functions in addition to a general cognitive/intellectual assessment.

In the age group of 3 to 30 months, we used 2 well-standardized and reliable measures, the Bayley Scales of Infant Development25 and the Vineland Adaptive Behavior Scale-Revised.23 For ages 30 months to 18 years, general cognitive development was assessed with...
the Stanford Binet IV. Six core tests that spanned the age ranges of interest were selected from this tool: vocabulary, comprehension, bead memory, quantitative, pattern analysis, and memory for sentences. Adaptive functioning was assessed by administering the Vineland Adaptive Behavior Scale–Revised to the primary caregiver. Receptive language was assessed by the Peabody Picture Vocabulary–Revised, which provided normative data by gender for ages 30 months and older. Visual motor development was determined by the Beery-Buktenica Test of Visual Motor Integration. This core neurobehavioral test battery required ~1.5 hours of direct behavioral assessment, and ~1 hour was required for parent/caregiver interview.

**Neurophysiological Evaluation**

An electroencephalogram (EEG) and cranial MRI scanning (evaluated by a neuroelectrophysiologist and a neuroradiologist, respectively) were performed at baseline. The MRI was routinely repeated at the end of the study, but the EEG was not. However, the physician who was caring for the patient could choose to repeat either of these studies as part of ongoing clinical management. The MRI and EEG were not repeated at regular intervals for several reasons. MRI scanning is particularly expensive and would increase third-party costs significantly. Testing reliability, evanescent abnormalities, and data analysis also represent confounding problems. Complicated safeguards would need to be built into the study design to ensure quality control of these measures, again adding costs to the study. The Steering and Planning Committee, after weighing these issues, concluded that these tests had limited heuristic value within the design of the protocol but believed it was important to assess the extent of neurologic disease before enrolling patients into the trial.

Evoked potentials and nerve conduction were selected as the serial neurophysiological measures of nervous system function. Visual evoked potentials have limited value in this population because of the young age and the lack of cooperation, so they were not performed. The brainstem auditory evoked potentials and the somatosensory evoked potentials studies are more reliable and provide objective measures of central nervous system dysfunction and of altered function related to DCA treatment. The protocol was used in accordance with the proposed revised American EEG Society guidelines for evoked potentials recording. For somatosensory evoked potentials testing, right and left median and posterior tibial nerve evoked potentials were performed under standard conditions in a darkened, quiet room. Chloral hydrate (50–75 mg/kg) was administered orally to promote conscious sedation or sleep. Brainstem auditory evoked potentials were conducted after right and left ear stimulation under the same conditions.

**Nerve Conduction**

Sensory and motor nerve conduction was selected as a serial measure of peripheral nervous system function and was conducted and scored by a clinical neurologist who directs these studies at the University of Florida. Repeated measures of peripheral nerve functional integrity were deemed important for several reasons. First, DCA is known to be a peripheral neurotoxin in 3 species, including humans. Second, patients with congenital lactic acidosis are at risk for developing a peripheral neuropathy as part of the disease process. Finally, the integrity of the central evoked potential depends on the propagation of stimulus along the peripheral sensory pathway. The presence of a peripheral neuropathy could obscure this observation and lead to possible misinterpretation of the evoked potentials.

**Other Quality-of-Life Measures**

Little attention has been paid to the development or application of quality-of-life measures among pediatric or adolescent patients, including those with congenital lactic acidosis. Therefore, we elected to develop our own set of quality-of-life questionnaires that would be relevant to children who were enrolled in our trial. Items were developed after interviews with parents of children who have congenital lactic acidosis and were evaluated at the University of Florida as well as with physicians, nurses, and psychologists who had treated or evaluated these patients. Two questionnaires were developed: a parent report form and a nurse report form. The parent report consistent of items that cover physical and behavioral changes observed in a child or in caring for the child at home, whereas the nurse report form included items that relate to similar physical and behavioral changes in the child observed in the GCRC. The initial version of these questionnaires was administered to nurses, mothers of healthy children, and mothers of children with cognitive impairments, including those caused by congenital lactic acidosis. As a result, the working models were modified into the versions used in the trial. The parent evaluation was administered at each admission to the GCRC as well as once at the midpoint between scheduled admissions. The nurse form was completed by the nurse coordinator within 48 hours after each admission, having observed each patient for parts of at least 2 nursing shifts.

**Patient Accounting**

Twenty-one patients were randomly assigned at month 0 to DCA (Fig 2). Five were lost to death or dropout by month 12 (4 in the 6-month preconditioned phase and 1 in month 7). Twenty-two patients entered on the placebo arm. Two were lost by month 12 (1 in the run-in period and 1 in month 7). Thirty-six patients were used in the efficacy and secondary analyses (33 who com-
completed the 12-month and 3 who completed the 9-month evaluations).

**Statistical Methods**

The primary efficacy comparison used the overall Global Assessment of Treatment Efficacy (GATE) score. The initial intent was to base this on the 5 independent raters (ophthalmologist, neuropsychologist, neurologist, nurse, and pediatrician). However, the ophthalmologist and neuropsychological evaluations were not done on 13 and 15 of the 36 assessable entrants, respectively. Hence, out of concerns for selection bias and after approval by the DSMB, these evaluations were not used in the overall GATE score analysis. The primary analysis was based only on the GATE scores of the neurologist, nurse, and treating pediatrician, using the mean of these 3 scores. Each patient was compared with baseline on the following scale: 1, improved considerably; 2, improved; 3, improved slightly; 4, not changed; 5, worsened slightly; 6, worsened; and 7, worsened considerably. We used the generalized odds ratio (GOR) for analysis. The GOR estimated by the quotient of (1) number concordant plus half the number of ties to (2) number of discordant plus half the number of ties. A value of 1.00 is the point of equivalence between the treatments. Values <1.00 favor placebo, whereas values >1.00 favor DCA. We determined the point estimate and 95% confidence intervals for the GOR. \( P \) values were calculated by the Wilcoxon test. A retrospective power calculation, which takes into account the need to change the basis of the primary end point from 5 to 3 evaluators, indicates that under an approximate normally distributed GATE score, the study is sensitive to a 1.0-SD difference in overall GATE scores (1.3 units), at \( P = .05 \) two-sided and 80% power. Secondary comparisons used 2-sample, 2-sided \( t \) tests.

**RESULTS**

**Clinical Characteristics of Patients**

Tables 1 and 2 summarize the diagnostic and clinical characteristics of the patients at the time of entry. A deficiency in the PDC was the single most common cause of congenital lactic acidosis among our patients (26%). Eleven (26%) patients were administered 1 or more anticonvulsant medications; 17 (40%) patients had a history of seizures, 2 of whom were treated with valproic acid. Thirty-five (79%) patients were taking 1 or more nutritional supplements, including sodium bi-
carbonate. The most common of these were preparations of coenzyme Q₁₀ (18 patients), carnitine (14 patients), vitamin B₁ or C (10 patients each), and citrate buffer (5 patients). Twenty-four (56%) patients were below the fifth percentile by height or weight or both. Most patients had some degree of psychomotor delay or hypotonioa or both. Pathologic findings from MRI of the brain was obtained in 41 patients within 12 months of randomization and included focal or diffuse atrophy (23 patients), hypogenesis or agensis of the corpus callosum (4 patients), evidence of ischemic necrosis (3 patients), and T2-weighted images consistent with or suggestive of Leigh syndrome (6 patients). MRI of the brain was normal in 7 patients. Physical examination disclosed evidence of peripheral sensory or motor neuropathy or both in 21 (49%) patients. The results of standard median peroneal motor nerve conduction studies and median and sural nerve sensory conduction studies that were performed on each patient at entry have been reported.³⁰ Intermittent constipation or diarrhea or both occurred in 12 (25%) patients. Nine (21%) patients had elevated serum concentrations of aspartate aminotransferase (reference: 15–46 μL) or alanine aminotransferase (reference: 11–66 μL) or both. Nineteen (44%) patients had electrocardiographic or echocardiographic signs of cardiac dysfunction. The most common abnor-

### TABLE 1 Patient Diagnoses and Demographics

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<tr>
<th>Patient</th>
<th>Diagnosis, Deficiency of</th>
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<td>&lt;5</td>
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<td>&lt;50</td>
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<td>M</td>
<td>13.0</td>
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</table>

Complex I, etc indicates deficiency of ≥1 respiratory chain complexes; OXPHOS, generalized reduction in respiratory chain enzyme activities; MERRF, mitochondrial encephalopathy and ragged red fibers.
mality was hypertrophy of the right or left ventricle or both (9 patients). All patients had some degree of abnormal renal function, established by the presence of previously published criteria.23

Acid-Base Status
Most patients had mild lactic acidosis in the basal state at entry. The mean whole-blood venous pH was 7.36 ± 0.06, the venous whole-blood lactate level was 2.2 ± 1.6 mmol/L, the serum bicarbonate level was 18.8 ± 3.7, and the anion gap was 15 ± 4. The CSF lactate, obtained in 32 patients, averaged 4.3 ± 1.9 mmol/L. A higher concentration of CSF lactate, compared with venous blood lactate, is a frequent finding in patients with congenital lactic acidosis.34

Other Chemistries
The hematocrit was <33% or the hemoglobin was <10.5 g/L or both in 8 (19%) patients. Anemia, when present, was usually normochromic and normocytic. Two (5%) patients had mild thrombocytopenia, defined as a platelet count <150/mm3. Twenty-one (49%) patients had hyperchloremia (serum chloride >104 mmol/L) in association with metabolic acidosis. Eight of the 11 patients with PDC deficiency had been consuming diets that were high in fat (55 ± 18% of total energy intake; range: 29–77%) and low in carbohydrates (31 ± 20%) before entry. Accordingly, serum ß-hydroxybutyrate concentrations in PDC-deficient children were increased (1.07 ± 1.36 mmol/L; normal, ≤0.16 mmol/L). However, the mean ß-hydroxybutyrate level in 32 children with a respiratory chain defect or a mutation in mtDNA also was modestly elevated (0.39 ± 0.39 mmol/L), although their mean dietary fat (35 ± 10%; range: 8–59%) and carbohydrate (53 ± 11%) energy intakes were typical of average diets. For most patients, remaining serum levels of electrolytes, creatinine, urea nitrogen, protein, albumin, thyrotropin, lipids, and lipoproteins were normal.

Lactate was measured in the urine of 35 patients and correlated modestly with the blood lactate concentration (r = 0.36; P = .069). Eleven of 41 patients had ketonuria, and 1 patient had oxaluria (oxalate: 254 mmol/mol creatinine; reference: 0–54 mmol/mol creatinine) in combination with excretion of multiple TCA cycle intermediates. The creatinine clearance was measured in 34 patients and averaged 102 ± 45 mol/min per 1.73 minutes2 on study entry, which was near the lower limit of normal when matched for age. Four children had proteinuria and 3 patients had glucosuria on urinalysis. Such findings have been reported previously in children with genetic mitochondrial disorders and may reflect glomerular and tubular dysfunction as a result of abnormal cellular energetics in these tissues.35

Bone and Mineral Metabolism
Plain films of the hands revealed demineralization or retarded bone age or both in 10 (23%) patients. These children had normal serum concentrations of phosphate, 25-hydroxy vitamin D, 1,25-hydroxy vitamin D and parathyroid hormone. A few other patients had mild abnormalities in these indices. One child had radiographic evidence of rickets and hypercalcuria (calcium: 8.3 mg/kg per day) but had normal serum levels of calcium and vitamin D.

Treatment Effects
There were no significant differences in GATE scores, expressed as GOR, after 6 months in the DCA-treated versus placebo group (Fig 3). There was no significant difference according to the separate blinded assessments of the neurologist, nurse, or pediatrician or their overall combined assessments. In addition, no differences were noted in neurologic or neurobehavioral development, the frequency or severity of intercurrent illnesses, pa-
Few adverse events were reported by patients or their family members or their local physicians during months 6 to 12 of the trial. Dropouts as a result of death or other reasons did not differ significantly between groups. Deaths during the study were determined to be attributable to the primary underlying disease. Withdrawals resulted from inability of the patient to travel to the study site because of disease progression. Five patients in the DCA arm reported 1 of the following: excessive sleepiness and lethargy; peripheral neuropathy; muscular rigidity of an upper extremity; brief, intercurrent hospitalization for disease exacerbation; and hand tremor. Four patients in the placebo arm reported 1 of the following: dehydration associated with low serum bicarbonate concentration, fever (102.1 °F), seizures with stroke-like event (1 patient with MELAS), and exacerbation of lactic acidosis.

Serial electrocardiographic and nerve conduction monitoring and measurement of vital signs and serum and urine chemistries disclosed no evidence of rhythm disturbances or blood pressure, heart or respiratory rate, nerve conduction, or biochemical abnormalities related to the administration of either agent. Specifically, there was no difference between treatment groups in mean serum concentrations of transaminases or other indices of hepatic function or in mean conduction amplitude or velocity in peripheral sensory or motor nerves.

During the course of this trial, we discovered that DCA alters tyrosine metabolism by inhibiting maleylacetate isomerase (Fig 4), which also dechlorinates n-levulinate, which potentially are toxic to liver and peripheral nerves. DCA administration led to a modest (1.5-fold) increase in urinary maleylacetate concentration after the carbohydrate challenge (Table 3). There were no significant differences in CSF lactate levels between the treatment groups or noteworthy differences in this index suggested by exploratory analyses of subgroups of patients who were categorized as having PDC deficiency, respiratory chain deficiency, or a mtDNA mutation.

Monitoring and Safety of Treatment

There were no instances in which the treatment code was broken or the patients or caregivers became aware of the treatment. All patients who were randomly assigned to receive DCA had measurable concentrations of this agent. The mean plasma kinetics of DCA differed markedly between the first dose and the final dose (Table 4).

TABLE 3

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Blood Lactate Response to Carbohydrate Meal Challenge</th>
<th>Blood Lactate, mmol/L</th>
<th>Difference</th>
<th>Month 6</th>
<th>Month 12</th>
<th>Difference</th>
<th>P</th>
<th>0.1</th>
<th>0.05</th>
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</thead>
<tbody>
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<td>Placebo</td>
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<td>2.06 ± 1.25</td>
<td>1.94 ± 0.95</td>
<td>0.12</td>
<td>0.012</td>
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<td></td>
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<tr>
<td>DCA</td>
<td></td>
<td>2.84 ± 1.25</td>
<td>1.64 ± 0.98</td>
<td>1.20</td>
<td>0.012</td>
<td>&lt; 0.001</td>
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</tbody>
</table>

The meal challenge test is described in “Methods.” Depicted are means ± SD of venous blood lactate levels obtained 1 hour after the meal was consumed.

TABLE 4

<table>
<thead>
<tr>
<th>Months on DCA</th>
<th>Half-Life, h</th>
<th>AUC, (µg/mL)*h</th>
<th>Cmax, µg/mL</th>
<th>Cmin, µg/mL</th>
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<td>Treatment</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCA</td>
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<td>1.42 ± 0.42</td>
<td>30.11 ± 17.43</td>
<td>19.51 ± 16.75</td>
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<tr>
<td></td>
<td>6</td>
<td>9.94 ± 7.90</td>
<td>611.27 ± 984.68</td>
<td>51.18 ± 63.75</td>
</tr>
</tbody>
</table>

Data are mean ± SD. AUC indicates area under the concentration curve; Cmax, maximum concentration; Cmin, minimum (dosing interval) concentration.

The results of this controlled trial are noteworthy in relation to those of a recent open-label investigation of 37 patients with proven or suspected genetic mitochondrial diseases. Patients in that study ranged in age from 0.6 to 53.1 years, and most were treated initially with daily oral DCA at a dose of 25 mg/kg or 50 mg/kg, with...
variable adjustment of dosage thereafter. The duration of treatment averaged 3.25 years. DCA treatment was associated with trends toward improvement in clinical symptoms, decreases in blood and cerebrospinal lactate concentrations, worsening of serum levels of liver transaminases, and a modest (~10%) incidence of worsening nerve conduction. As expected (cf refs 12 and 33), repeated DCA administration decreased plasma clearance of the drug. DCA could be measured in CSF, as reported previously (reviewed by Stacpoole6).

DISCUSSION
The rationale for this controlled clinical trial of DCA therapy was based on its effects in open clinical studies of patients with congenital lactic acidosis, in whom clinical and biochemical improvements were reported. In virtually all tissues, DCA is a potent activator of the PDC. In theory, this effect should reduce circulating and cellular lactate concentrations and stimulate mitochondrial oxidative metabolism and energetics in cells that contain mitochondria with functional respiratory chain enzymes.9 The results of many in vitro and whole-animal experiments are consistent with this notion.

We found that DCA, as predicted, was superior to placebo in reducing the blood lactate response to a carbohydrate challenge but did not alter basal lactate concentrations or any clinically important outcome variable. Thiamine is a requisite co-factor for PDC, and all

FIGURE 4
Tyrosine catabolic pathway and site of action of DCA. DCA depletes maleylacetocetate isomerase (MAAI), causing accumulation of maleylacetoacetate, maleylacetone, fumarylacetocetate, and fumarylacetone. MAAI is identical to the ζ isoform of glutathione S-transferase (GSTζ2), which biotransforms DCA to glyoxylate. Succinylacetone also accumulates as a result of DCA and is a known inhibitor of δ-aminolevulinate dehydratase, causing buildup of δ-aminolevulinate and inhibition of heme biosynthesis. Perturbation of heme metabolism is thought to cause the neuropathic complications in patients with tyrosinemia.

FIGURE 5
Urinary excretion of maleylacetone (MA) and δ-aminolevulinate (δ-ALA) in 43 children with congenital lactic acidosis. All patients received placebo (P) for the first 6 m. At 6 months, 22 patients were crossed over to receive 25 mg/kg per day DCA (D) and were followed for an additional 6 months. Data are mean ± SD of 24-hour excretion of analyte. MA excretion in the DCA group (N = 22) is ninefold higher than in the placebo group (N = 21) at 12 months, relative to the excretion of MA at 6 months (N = 43).
patients received some thiamine during the course of this trial. Therefore, there is a theoretical possibility that thiamine supplementation contributed to the observed changes in circulating lactate.

We also found that chronic DCA was well tolerated and, contrary to expectations, showed no evidence of toxicity to the liver or peripheral nervous system during a 6-month period of exposure, despite inducing marked changes in its plasma kinetics and in tyrosine metabolism. This is in striking contrast to the recently reported high incidence of drug-induced peripheral neuropathy in 30 patients who had the A3243G mutation for MELAS and were enrolled in a controlled crossover trial of oral DCA, administered as a twice-daily dose of 12.5 mg/kg per day in capsule form. The mean age of the patients in that study was 30 years, and 10 patients had some evidence of glucose intolerance. We enrolled 6 children (age: 6–19.1 years) with MELAS (5 of whom had the A3243G mutation); none had glucose intolerance, and all tolerated DCA well. It is intriguing to speculate that these apparent discrepancies in tolerance to chronic DCA reported here and by Kaufmann et al may reflect age-dependent differences in the kinetics and biotransformation of DCA or in its impact on tyrosine and heme metabolism. The adverse effects of chronic hyperglycemia on nerve function also may have contributed to the high frequency of peripheral neuropathy in the older MELAS population. There are other anecdotal reports of peripheral neuropathy occurring in a few children who had genetic mitochondrial diseases and were treated for several months or years with DCA. However, peripheral nerve conduction abnormalities are common underlying manifestations of these diseases, so the true incidence of peripheral neuropathy that is attributable to DCA in patients who are treated chronically with the drug is unknown.

It has been well established that DCA inhibits its own metabolism in rodents and humans on repeat dosing and over a wide concentration rage as a result of its metabolism in rodents and humans on repeat dosing and treated chronically with the drug is unknown. Ropatry that is attributable to DCA in patients who are the predicted effect on the activity and expression of malic enzyme and malic enzyme isomerase, which is identical in humans to the H<sub>2</sub> family isoform of glutathione S-transferase. However, it has not been established that there are clear associations between changes in the plasma kinetics and biotransformation of DCA and either its pharmacodynamics or its toxicity. We found no obvious relationship between the kinetic indices in this trial (Table 4) and other clinical or biochemical measurements. Therefore, the predictive value of plasma DCA concentrations or other kinetic indices in determining chronic safety or efficacy has yet to be determined.

This is the first controlled trial of DCA for congenital lactic acidosis. Because of the rarity of this fatal disease and the reported beneficial effects of DCA on such patients, regardless of genotype, we recruited a heterogeneous group of children that included a wide spectrum of causes and complications of congenital lactic acidosis. This decision was based on the premise that the common pathologic denominator of these inborn errors was inhibition of mitochondrial energy metabolism that could be mitigated by the ability of DCA to stimulate the activity of the PDC, which controls the rate of aerobic glucose (and lactate) oxidation in all cells.

It is possible that the initiation of DCA therapy earlier in the course of illness or its administration to discrete populations at a higher dose than we used would improve outcome in patients like those we studied. Most patients with very low levels of residual PDC or respiratory chain complex enzyme activity develop fulminant lactic acidosis and die within days or a few weeks of birth. In others, the disease may be more chronic and its diagnosis delayed months or years until appropriate clinical suspicion is raised. By that time, extensive and irreversible end-organ damage may have occurred. These represent major challenges in the evaluation of any putative therapy. Nevertheless, our study provides a useful template with which to design future rigorously controlled clinical trials for the treatment of congenital lactic acidosis.

ACKNOWLEDGMENTS

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We thank the patients and their families for participation; the dedicated staff of the GCRC, the pilots and staff of Mercy Medical Airlift and Angel Flight of Florida for facilitating patient transport; the members of the DSMB (Stephen Cederbaum, Chairman, Elizabeth Wright, John McReynolds, and Patricia Huff) for outstanding contributions to the integrity of this trial; and Candace Caputo and Lesa Gilbert, RN, for administrative assistance.

REFERENCES


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Controlled Clinical Trial of Dichloroacetate for Treatment of Congenital Lactic Acidosis in Children


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