Letters to the editors

Eur J Pediatr (1993) 152:537–541

European Journal of
Pediatrics

Beneficial effect of sodium dichloroacetate in muscle cytochrome C oxidase deficiency

A. B. Burlina[1], O. Milanesi[1], P. Biban[1], A. Bordugo[1], B. Garavaglia[2], F. Zacchello[1], S. Di Mauro[3]

[1]Dipartimento di Pediatria, Università di Padova, Via Giustiniani 3, I-35128 Padova, Italy
[2]Divisione di Biochimica e Genetica, Istituto Neurologico "Besta", Milano, Italy
[3]Neurological Institute, Columbia-Presbyterian Medical Center, New York, USA

Received: 30 November 1992 / Accepted: 4 January 1993

Sir: Severe lactic acidosis is a biochemical marker found in hypoxia, and in congenital disorders of gluconeogenesis, pyruvate and NADH-oxidation. Many patients with these inherited defects die or show growth and psychomotor retardation because standard treatment of these disorders is unsatisfactory [1]. Dichloroacetate (DCA) is known to inhibit the pyruvate dehydrogenase-specific kinase in various tissues and it has a lactate-lowering effect in patients with chronic congenital lactic acidosis [2, 4]. Here, we report the successful treatment of severe lactic acidosis associated with hypertrophic cardiomyopathy in a patient with muscle cytochrome c oxidase (COX) deficiency.

The patient was born at term to non-consanguineous healthy parents (birth weight 2700 g; Apgar scores 9 and 10 at 1 and 5 min). At the age of 1 month he was admitted to a local hospital because of rapid respiration, feeding difficulty, weakness, and lack of ocular fixation. The liver was 5 cm below the costal margin and he had severe metabolic acidosis with elevated blood lactate (5.5 mmol/l). ECG showed signs of ischaemia and echocardiography showed marked hypertrophic cardiomyopathy.

He was transferred to our department in a critical condition (polypnoic and dyspnoic) and a repeat ECG showed marked hypertrophy of the left ventricular posterior wall (diastolic thickness 8.5 mm, normal value 4–6 mm), reduced diastolic left ventricular function and mild pericardial effusion. Blood chemistry showed normoglycaemia and severe metabolic acidosis (pH 7.18, HCO_3 8; lactate 15 mmol/l, reference value <2 mmol/l; pyruvate 0.35 mmol/l, reference value <0.16 mmol/l; lactate/pyruvate molar ratio 42; 3-hydroxybutyrate 0.55 mmol/l, reference value <0.06; acetoacetate 0.12 mmol/l, reference value <0.02; 3-hydroxybutyrate/acetoacetate molar ratio 4.58); urinary organic acid screening revealed increased excretion of lactic acid (4800 mmol/mol creatinine, reference <200), 2-hydroxybutyric acid (55 mmol/mol creatinine, reference <2), 3-hydroxybutyric acid (212 mmol/mol creatinine, reference <2), fumaric 134 mmol/mol creatinine, reference <5), malic (74 mmol/mol creatinine, reference <5), α-ketoglutaric (165 mmol/mol creatinine, reference <10), and citric acid (325 mmol/mol creatinine, reference <20); serum total and free carnitine concentration were 56 and 44 μmol/l, respectively; total CPK was 216 U/l (normal <290) with normal CK-MB fraction.

He received large doses of carnitine and sodium bicarbonate without clinical benefit. Because of increasing lactate levels (18 mmol/l) and clinical worsening, DCA (Tokyo Kasey, Japan) was administrated orally in three doses (150 mg per day). After 3, 6, 9, 12 and 24 h, blood lactate levels were 18 and decreased to 12, 10, 6 and 1.8 mmol/l, respectively, and pyruvate from 0.37 to 0.14 mmol/l, then remained within the normal range although the dose of DCA was gradually decreased to 25 ng/kg per day within 7 days.

Abbreviations: COX = cytochrome C oxidase; DCA = dichloroacetate

On the 2nd day of DCA therapy a muscle biopsy was performed and revealed reduced activity in COX (18.9 nmol/min/mg; control 63 ± 29) and normal succinate cytochrome c reductase, citrate synthase, NADH dehydrogenase, succinate dehydrogenase and pyruvate dehydrogenase. After 16 days of oral administration of DCA, the drug was discontinued because of the improved clinical condition; 12 h later, however, the lactate level again increased to 15 mmol/l and remained between 14 and 18 mmol/l until DCA administration was resumed; thereafter lactate levels decreased to normal levels within 2 days. Furthermore, thiamine (1 mg/kg/day) was added because DCA, stimulating two thiamine-dependent enzymes (PDH and branched chain α-keto acid dehydrogenase complex), might induce a deficiency for this vitamin [3]. After 9 months of therapy, there has been a dramatic reduction of heart size: echocardiography showed a normal heart, with normal wall thickness (5 mm; controls 4–6 mm) and left ventricular function (ejection fraction 76%, systolic fraction 43%) and low blood lactate values ranging from 1.6 to 3.1 mmol/l. Because it is thought that DCA is metabolised to oxalate and glyoxalate in liver we measured plasma oxalate which was normal (5 μmol/l; controls <7); The child is developing normally, both physically and mentally; EEG and auditory and somatosensory evoked potentials are normal.

Although experience with DCA therapy is still limited to few cases, this is the first patient with muscle COX deficiency who appears to have responded to this therapy. Two possible explanations can be proposed. The first is that COX deficiency in the child was due to a mitochondrial DNA defect, and muscle and liver had a mixture of normal and COX deficient mitochondria on the basis of heteroplasmy. If the proportion of normal mitochondria is adequate, activation of pyruvate dehydrogenase by DCA would stimulate degradation of lactate in peripheral tissues resulting in decreased lactic acidaemia. The second explanation is that DCA may improve cardiac output and left ventricular mechanical efficiency under conditions of myocardial ischaemia [3], probably by favouring myocardial metabolism of carbohydrate and lactate over fat metabolism.

Finally, to the best of our knowledge, there is no evidence that DCA should affect muscle COX activity in vivo (in vitro addition of drug does not alter COX activity in normal muscle; personal observation); only longitudinal studies comparing enzyme activities in muscle biopsies obtained before and during DCA treatment could answer this question directly.

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