Human Studies Involving DCA Use

Below are several papers that discuss the use of DCA in humans. In addition to the works shown here, there is a massive collection of research done on DCA gathered in the EPA’s "Toxicological Review of Dichloroacetic Acid", a 200 plus page volume listing a summary of most DCA safety and health research done as of August 2003.

Dichloroacetate as metabolic therapy for myocardial ischemia and failure.

Clinical Investigations

Bersin, Robert M. MD; Stacpoole, Peter W. PhD, MD

Abstract:
This article critically reviews the pharmacologic effects of the investigational drug dichloroacetate (DCA), which activates the mitochondrial pyruvate dehydrogenase enzyme complex in cardiac tissue and thus preferentially facilitates aerobic oxidation of carbohydrate over fatty acids. The pharmacologic effects of DCA are compared with other interventions, such as glucose plus insulin, inhibitors of long chain fatty acid oxidation and adenosine, that are also thought to exert their therapeutic effects by altering myocardial energy metabolism. Short-term clinical and laboratory experiments demonstrate that intravenous DCA rapidly stimulates pyruvate dehydrogenase enzyme complex activity and, therefore, aerobic glucose oxidation in myocardial cells. Typically these effects are associated with suppression of myocardial long chain fatty acid metabolism and increased left ventricular stroke work and cardiac output without changes in coronary blood flow or myocardial oxygen consumption. Although long-term studies are lacking, short-term parenteral administration of DCA appears to be safe and capable of significantly improving myocardial function in conditions of limited oxygen availability by increasing the efficient conversion of myocardial substrate fuels into energy.

Effects of dichloroacetate on exercise performance in healthy volunteers

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Abstract Dichloroacetate (DCA), a stimulator of the pyruvate dehydrogenase complex, decreases lactate levels and peripheral resistance and increases cardiac output. This study was performed to examine the effects of DCA on exercise performance in humans. Eight healthy male volunteers (age 20–28 years) were tested by bicycle spiro-ergometry using a microprocessor-controlled gas analysis system after infusion of DCA (50 mg/kg body weight) or saline. Prior infusion of DCA significantly reduced the increase of lactate levels during exercise when compared with infusion of saline (1.40±0.21 vs 2.10±0.09 mmol·l−1 at 50% of the expected maximal working capacity, P<0.05; 8.53±0.45 vs 9.92±0.59 mmol·l−1 at maximal working capacity, P<0.05). Oxygen uptake increased significantly after DCA when compared with saline from 7.5±0.4 vs 7.4±0.5 to 27.2±1.5 vs 23.7±1.7 (P<0.05) at anaerobic threshold and to 35.6±1.7 vs 30.5±1.0 ml · kg−1 · min−1 (P<0.05) at maximal exercise capacity. Following DCA infusion the workload at which the anaerobic threshold was
reached was significantly higher (160±7 vs 120±5 W, P<0.05) and the maximal working capacity was significantly increased (230±9 vs 209±8 W, P<0.05). In summary, DCA reduced the increase of lactate levels during exercise and increased oxygen uptake at the anaerobic threshold and at maximal working capacity, which was significantly increased. These results warrant further studies on a potential therapeutic application of DCA in patients with reduced exercise capacity.

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Metabolic effects of dichloroacetate in patients with diabetes mellitus and hyperlipoproteinemia

PW Stagpoole, GW Moore, and DM Kornhauser

Abstract

Dichloroacetate is known to reduce plasma glucose and triglycerides in diabetic and starved animals and to lower plasma lactate under various experimental conditions. To investigate its metabolic effects in man, we administered oral doses (3 to 4 g) of dichloroacetate as the sodium salt to patients with diabetes mellitus or hyperlipoproteinemia or both for six to seven days. Dichloroacetate significantly reduced fasting hyperglycemia an average of 24 per cent (P less than 0.01) from baseline and produced marked, concomitant falls in plasma lactate (73 per cent; P less than 0.05 to less than 0.01) and alanine (82 per cent; P less than 0.01 to less than 0.001). In addition, it significantly decreased plasma cholesterol (22 per cent; P less than 0.01 to less than 0.001) and triglyceride (61 per cent; P less than 0.01) levels while increasing (71 per cent; P less than 0.01) plasma ketone-body concentrations. Plasma insulin, free fatty acid and glycerol levels were not affected. Serum uric acid rose, whereas excretion and renal clearance fell. Some patients experienced mild sedation, but no other laboratory or clinical evidence of adverse effects was noted during or immediately after the treatment phase.

Clinical Investigation

Sodium dichloroacetate treatment of children with mitochondrial encephalomyopathies

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This is copied from the discussion portion of the paper: The recommended therapeutical range of DCA dosage in children is 100-150 mg DCA/kg/day should be well tolerated. Nevertheless, DCA therapy can be problematic in some cases. It has been reported that after DCA treatment (100 mg/kg) for 20 weeks, a girl with mitochondrial encephalomyopathy developed distal polyneuropathy. This was reversible and disappeared after termination of DCA treatment [38]. According to our experience, however, efficient decreases of blood lactate levels can be achieved by lower DCA dosages.

Therapy of complex I deficiency: peripheral neuropathy during dichloroacetate therapy.


A therapeutic trial with polyvitamins and dichloroacetate (DCA) in combination with thiamine in a 13-year-old girl with complex I deficiency is reported. The polyvitamin therapy included thiamine, riboflavin, ascorbate, coenzyme Q 10 and carnitine. This therapeutic regime was used over a period of 17 months without any effect. Although DCA lowered the lactate concentration in blood and CNS—measured by magnetic resonance spectroscopy—no clinical benefit was achieved. After 20 weeks of DCA therapy a distal polyneuropathy with areflexia developed although 100 mg thiamine daily as comedication was given from the beginning of DCA therapy. Nerve conduction velocity of the peroneal nerve was not detectable, sensible evoked potentials of the tibialis posterior nerve were normal. This side-effect resolved completely within 6 months after omission of DCA. Our observation suggests a direct toxic effect of DCA only on the peripheral nervous system in our patient since several cerebral MRI and magnetic resonance spectroscopy studies showed no abnormalities.

CONCLUSION. DCA lowers the lactate concentration in children with complex I deficiency of the respiratory chain in a dose of 100 mg/kg body weight without clinical benefit. Reversible peripheral polyneuropathy may develop under DCA therapy despite thiamine medication.

Dichloroacetate and cerebral ischaemia therapeutics

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Brain ischaemia is a major medical problem which totally lacks meaningful therapeutic options. A drug that reduces morbidity and mortality associated with head injury and stroke would constitute a major medical breakthrough. Although many mechanistic approaches have been evaluated clinically for both stroke and head injury, none have yet to be proven successful. Dichloroacetate (DCA, Ceresine™) is a small molecule that activates pyruvate dehydrogenase (PDH) and crosses the blood-brain barrier. PDH activation reduces neurotoxic lactic acidosis which always accompanies brain ischaemia. DCA shows substantial efficacy in a variety of models of stroke, pre-stroke, head or spinal cord injury. Agents that lower cerebral lactic acidosis have not yet been clinically evaluated in head injury and stroke, although DCA has been shown clinically to reduce ambient lactate concentrations in patients with such conditions. DICHA has also been shown to be well-tolerated in these patients, and unlike many halogenated molecules, is not mutagenic. Since elevated brain lactate is correlated with poor outcome in both preclinical and clinical studies, an agent such as DCA may prove to reduce the brain injury associated with these disorders. Potential clinical applications of DCA include stroke, head injury, spinal cord injury, and chronic disorders such as congenital lactic acidosis (CLA) and mitochondrial lactic acidosis and stroke-like syndrome (MELAS)

Dichloroacetate causes reversible demyelination in vitro: potential mechanism for its neuropathic effect.

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Dichloroacetate (DCA) is an investigational drug for genetic mitochondrial diseases whose use has been mitigated by reversible peripheral neuropathy. We investigated the mechanism of DCA neurotoxicity using cultured rat Schwann cells (SCs) and dorsal root ganglia (DRG) neurons. Myelinating SC-DRG neuron co-cultures, isolated SCs and DRG neurons were exposed to 1-20 mM DCA for up to 12 days. In myelinating co-cultures, DCA caused a dose- and exposure-dependent decrease of myelination, as determined by immunolabeling and immunoblotting for myelin basic protein (MBP), protein zero (P0), myelin-associated glycoprotein (MAG) and peripheral myelin protein 22 (PMP22). Partial recovery of myelination occurred following a 10-day washout of DCA. DCA did not affect the steady-state levels of intermediate filament proteins, but promoted the formation of anti-neurofilament antibody reactive whirls. In isolated SC cultures, DCA decreased the expression of P0 and PMP22, while it increased the levels of p75(NTR) (neurotrophin receptor), as compared with non-DCA-treated samples. DCA had modest adverse effects on neuronal and glial cell vitality, as determined by the release of lactate dehydrogenase. These results demonstrate that DCA induces a reversible inhibition of myelin-related proteins that may account, at least in part, for its clinical peripheral neuropathic effects.

Link to full text of article

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Human Kinetics of Orally and Intravenously Administered Low-Dose 1,2-13C-Dichloroacetate.

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Dichloroacetate (DCA) is a putative environmental hazard, owing to its ubiquitous presence in the biosphere and its association with animal and human toxicity. We sought to determine the kinetics of environmentally relevant concentrations of 1,2-(13)C-DCA administered to healthy adults. Subjects received an oral or intravenous dose of 2.5 mug/kg of 1,2-(13)C-DCA. Plasma and urine concentrations of 1,2-(13)C-DCA were measured by a modified gas chromatography-tandem mass spectrometry method. 1,2-(13)C-DCA kinetics was determined by modeling using WinNonlin 4.1 software. Plasma concentrations of 1,2-(13)C-DCA peaked 10 minutes and 30 minutes after intravenous or oral administration, respectively. Plasma kinetic parameters varied as a function of dose and duration. Very little unchanged 1,2-(13)C-DCA was excreted in urine. Trace amounts of DCA alter its own kinetics after short-term exposure. These findings have important implications for interpreting the impact of this xenobiotic on human health.

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Dichloroacetate causes toxic neuropathy in MELAS
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A randomized, controlled clinical trial

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Objective: To evaluate the efficacy of dichloroacetate (DCA) in the treatment of mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS).

Background: High levels of ventricular lactate, the brain spectroscopic signature of MELAS, correlate with more severe neurologic impairment. The authors hypothesized that chronic cerebral lactic acidosis exacerbates neuronal injury in MELAS and therefore, investigated DCA, a potent lactate-lowering agent, as potential treatment for MELAS.

Methods: The authors conducted a double-blind, placebo-controlled, randomized, 3-year cross-over trial of DCA (25 mg/kg/day) in 30 patients (aged 10 to 60 years) with MELAS and the A3243G mutation. Primary outcome measure was a Global Assessment of Treatment Efficacy (GATE) score based on a health-related event inventory, and on neurologic, neuropsychological, and daily living functioning. Biologic outcome measures included venous, CSF, and 1H MRSI-estimated brain lactate. Blood tests and nerve conduction studies were performed to monitor safety.

Results: During the initial 24-month treatment period, 15 of 15 patients randomized to DCA were taken off study medication, compared to 4 of 15 patients randomized to placebo. Study medication was discontinued in 17 of 19 patients because of onset or worsening of peripheral neuropathy. The clinical trial was terminated early because of peripheral nerve toxicity. The mean GATE score was not significantly different between treatment arms.

Conclusion: DCA at 25 mg/kg/day is associated with peripheral nerve toxicity resulting in a high rate of medication discontinuation and early study termination. Under these experimental conditions, the authors were unable to detect any beneficial effect. The findings show that DCA-associated neuropathy overshadows the assessment of any potential benefit in MELAS.

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A controlled clinical trial of dichloroacetate for treatment of lactic acidosis in adults. The Dichloroacetate-Lactic Acidosis Study Group


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 > or = 5.0 mmol per liter and either an arterial-blood pH of < or = 7.35 or a base deficit of > or = 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.
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 -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.

Review article

The pharmacology of dichloroacetate

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Abstract

Dichloroacetate (DCA) exerts multiple effects on pathways of intermediary metabolism. It stimulates peripheral glucose utilization and inhibits gluconeogenesis, thereby reducing hyperglycemia in animals and humans with diabetes mellitus. It inhibits lipogenesis and cholesterolgenesis, thereby decreasing circulating lipid and lipoprotein levels in short-term studies in patients with acquired or hereditary disorders of lipoprotein metabolism. By stimulating the activity of pyruvate dehydrogenase, DCA facilitates oxidation of lactate and decreases morbidity in acquired and congenital forms of lactic acidosis. The drug improves cardiac output and left ventricular mechanical efficiency under conditions of myocardial ischemia or failure, probably by facilitating myocardial metabolism of carbohydrate and lactate as opposed to fat. DCA may also enhance regional lactate removal and restoration of brain function in experimental states of cerebral ischemia. DCA appears to inhibit its own metabolism, which may influence the duration of its pharmacologic actions and lead to toxicity. DCA can cause a reversible peripheral neuropathy that may be related to thiamine deficiency and may be ameliorated or prevented with thiamine supplementation. Other toxic effects of DCA may be species-specific and reflect marked interspecies variation in pharmacokinetics. Despite its potential toxicity and limited clinical experience, DCA and its derivatives may prove to be useful in probing regulatory aspects of intermediary metabolism and in the acute or chronic treatment of several metabolic disorders.

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