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LETTER TO THE EDITORS

Severe encephalopathy and polyneuropathy induced by dichloroacetate

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Dear Sirs,

In 2007, an article in the New Scientist presented dichloroacetate (DCA) as 'a cheap and safe drug that kills most cancers' [1]. This statement was based on the findings of Bonnet et al. (2007) [2], who showed that DCA induces apoptosis and decreases in vitro tumor growth in several cancer cell lines by shifting the metabolism of cancer cells from glycolysis to glucose oxidation. In the same study, DCA was administered to nude rats in the drinking water (75 mg/L, during 3 months) and could prevent and reverse tumor growth without apparent toxicity. Dichloroacetate was proposed as an attractive candidate for proapoptotic cancer therapy [3]. Without any clinical data, DCA was hailed as a 'miracle drug' on internet-based patient forums and has since been prescribed off-label by alternative physicians or bought directly by patients via webshops (http://www.puredca.com and http://www.pharma-dca.com). Recently, a small clinical study was performed in five glioblastoma patients treated with various DCA doses. Grade II and grade III polyneuropathy occurred in patients treated with DCA 25 mg/kg/day and 50 mg/kg/day, respectively. The maximum DCA dose at which none of the patients had a clinically significant peripheral neuropathy was 6.25 mg/kg orally, twice a day (12.5 mg/kg/day) for at least 3 months [4]. For the first time, we present a patient who developed encephalopathy and grade III sensorimotor polyneuropathy after 4 weeks of DCA treatment (15 mg/kg/day).

A 46-year old patient with melanoma which had metastasized to the lung and lymph nodes 2 years previously, was admitted to the Antoni van Leeuwenhoek Hospital in The Netherlands because of confusion and gait disturbance. Four weeks before admission he had started taking capsules with identified DCA (400 mg, thrice daily, corresponding with 15 mg/kg/day) and vitamin A capsules (150,000 IU/day), prescribed by an alternative physician. On neurological examination he showed impaired mental processing, dysarthria and an unsteady gait. MRI of the brain and serum blood tests were normal. In the following days he became more confused, showed aggressive behaviour, had visual hallucinations and dysphasia. Cerebrospinal fluid (CSF) examination demonstrated normal biochemical parameters, no malignant cells and negative PCRs for neurotrophic viruses. Antineuronal antibody screening was negative. Both the DCA and vitamin A capsules were stopped on the day of admission. The DCA concentration in the CSF on day 2 after hospital admission was 78 μg/mL, as measured by liquid chromatography tandem mass-spectrometry. On day 16, the DCA CSF concentration decreased to 11 μg/mL, indicating an elimination half-life for DCA in the CSF of approximately 5 days. No serum samples for DCA measurement were available.

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Meanwhile, the patient was treated with haloperidol and lorazepam. His confusional state improved within 2 weeks, but severe dysarthria remained. A bilateral facial nerve paresis (grade II), a profound sensory ataxia of arms and legs and a severe distal paresis of the legs were present on further neurological examination. He was unable to walk. Electromyography demonstrated a severe sensorimotor axonal polyneuropathy. In the following 8 months, all neurologic deficits gradually improved. Only a slight paresis of the foot extensors (MRC 5^{-}) but no cognitive deficits remained.

Most of our knowledge on DCA comes from randomized clinical trials in children and adults with lactic acidosis complicating mitochondrial diseases, who were treated with DCA (12.5 mg/kg twice a day). No significant clinical efficacy was seen in these patients, but reversible axonal polyneuropathy occurred in 10% of the children and 86% of the adults [5, 6]. This age-dependent DCA peripheral neurotoxicity was found to be due to an age-related decrease in plasma clearance of DCA, probably because of inhibition of the DCA metabolism on repeat dosing in adults [7].

In our patient, the DCA CSF concentration of 78 μg/mL, 2 days after cessation of DCA intake (15 mg/kg/day during 1 month), is even higher than the average maximal blood plasma concentrations (C_{max}) of 53 μg/mL (±18 μg/mL) measured in adults taking 12.5 mg/kg twice a day for 6 months [7]. It is therefore likely that DCA accumulation has occurred in our patient, resulting in severe neurologic side-effects. We can not exclude that the metabolism of DCA has been influenced by concurrent use of high dose vitamin A in our patient.

The presented patient illustrates that DCA administered in a recommended dose range can be highly neurotoxic, leading to encephalopathy and a disabling sensorimotor axonal polyneuropathy. As clinical data on the efficacy of DCA in cancer patients are lacking and serious neurological side effects can occur, we strongly advise the use of DCA in clinical trials only.

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