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Dimercaptosuccinic Acid in the Treatment of Depression Following Lead Exposure

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Long-term exposure to lead is known to cause a variety of neurotoxic manifestations, including symptoms of depression. Dimercaptosuccinic acid (DMSA), a recently approved oral chelating agent, can diminish the body burden of lead, but few cases of documented clinical improvement following treatment have been reported. We report a case of moderate to severe depression in a long-term lead worker that appeared to respond dramatically to DMSA. This response suggests a possible therapeutic role for DMSA in the treatment of depression in lead-exposed patients.

Key words: lead toxicity, DMSA, affective disorder, chelation

INTRODUCTION

Long-term exposure to lead is known to cause a variety of adverse cognitive, somatic, and affective disorders in adults, including deficits in memory, attention, visual-motor coordination, abstraction and concept formation; fatigue; headache; and mood and personality changes [Bornschein and Kuang, 1990; Agency for Toxic Substances and Disease Registry, 1990]. Several studies have found an association between lead exposure and depression [Baker et al., 1985; Schottenfeld and Cullen, 1984; Cullen et al., 1983].

The mainstay of treatment for lead toxicity is removal from exposure. When medical therapy is judged to be necessary, the drug of choice for years has been calcium disodium edetate (EDTA) [Rempel, 1989]. This chelating agent can reduce the body burden of lead [Chisholm, 1990], but its efficacy in improving neurobehavioral abnormalities following chronic exposure is not well established. Several case reports have suggested improvements in various neuropsychological test outcomes [Mapou and Kaplan, 1991; Linz et al., 1992], and one study has suggested improvement of a severe depression [Balestra, 1991].

More recently, dimercaptosuccinic acid (DMSA) has attracted considerable attention as a chelating agent. It offers several potential advantages over EDTA,

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including ease of administration (DMSA is an oral drug, while EDTA is given parenterally), increased efficacy for removing lead from soft tissue, and decreased toxicity [Graziano, 1986; Fournier et al., 1988; Cory-Slechta, 1988; Aposhian and Aposhian, 1990]. DMSA has been approved by the U.S. Food and Drug Administration for treatment of lead toxicity in children. However, no randomized trials have as yet documented the efficacy of DMSA in treating adult lead toxicity, and clinical experience with this use of the agent remains relatively scanty. This report describes a case of moderate to severe depression in a lead worker that responded to DMSA therapy. It raises the possibility that DMSA may play a role in treating lead-related depression.

CASE REPORT

History of Present Illness

The patient was a 44-year-old man who was referred to the Environmental and Occupational Medicine Program in February, 1992, for evaluation of possible toxic effects of occupational exposure to lead. At that time, he was complaining of depressed mood, fatigue, inability to concentrate, anhedonia, nightmares, and early morning awakening that had developed and progressively worsened over ~ 1 year. He had stopped participating in sports and serving as a local Little League coach during the months prior to presentation. In addition, he complained of memory loss and irritability and recently had been unable to find his car in the parking lot at work. In another episode, he had made his usual morning cup of coffee and taken it to the kitchen table only to find that he had already made a cup and placed it on the table minutes before. He described yelling at family members for what he recognized to be minor offenses, and indicated that doing so was a change in his behavior. He denied loss of appetite and weight change.

In January, 1992, he had consulted a psychiatrist who, on the basis of the symptoms described above, diagnosed major depression and initiated treatment with desipramine. At the time of his initial evaluation at our clinic for possible lead toxicity, he had been treated for approximately 4 weeks and did not recognize any symptomatic improvement. Desipramine was discontinued by his psychiatrist after 10 weeks of treatment, and fluoxetine was begun. The patient reported improvement in his mood with the change in medication.

Past Medical History

His past medical history was remarkable for a motor vehicle accident at age 39 years that left him with residual left hip pain. The patient had no prior history of psychiatric disorders, nor did he have a family history of depression. He was taking no medications other than desipramine. He had completed 2 years of college. He was a nonsmoker and drank two beers daily.

Occupational History

His occupational history included military service from age 18 years to age 21 years, and work as a self-employed bricklayer from age 21 years to age 27 years. At age 27 years, he went to work at a lead battery manufacturing plant. Over the subsequent 17 years, he worked in most areas of the plant, including several that were known to be dusty. He had not used a respirator until 1 year prior to presentation, and

he typically wore his work clothes home without showering or changing them at the plant. He did wear gloves at work, but he habitually bit his fingernails and may therefore have sustained further exposure to lead by ingestion.

Quarterly blood lead levels over the duration of the patient's employment were reviewed. During the first 4 years of his employment, the levels had generally ranged from 2.0 to 3.0 μmol/liter (41–62 μg/dl), with occasional values slightly greater than that range. During the next 13 years, most of his blood lead levels were between 1.5 and 2.5 μmol/liter (31 and 52 μg/dl).

Review of Systems

The patient denied gastrointestinal or musculoskeletal symptoms other than the chronic left hip pain noted above.

Physical Examination

The patient was well groomed, pleasant, and cooperative. His blood pressure was 110/80 mm Hg, his pulse was 80 bpm, his respiratory rate was 12, and his temperature was 97.6°F. No gingival "lead line" was observed, and completely normal physical findings were present on examination of the hearts, lungs, and abdomen. Mental status examination revealed no psychomotor agitation or retardation. He described depressed mood and feelings of guilt but denied suicidal ideation. His associations were tight and logical. His affect was constricted to a dysphoric range. Neurologic examination revealed normal cranial nerve function, strength, sensation, cerebellar function, and deep tendon reflexes.

Laboratory Results

The hemoglobin was 161 g/liter (16.1 g/dl), the hematocrit 46.3%, and the red blood cell indices normal. The blood urea nitrogen was 4.6 mmol/liter of urea (13 mg/dl), the creatinine 132.6 umol/liter (1.5 mg/dl), and remaining chemistry values normal except for a slightly elevated cholesterol. Urinalysis was completely negative.

At the time of initial evaluation in our clinic, his blood lead level was 1.8 μmol/liter (37 μg/dl) and his free erythrocyte protoporphyrin was 72 μg/dl (normal range 0–71 μg/dl). Diagnostic chelation was performed by administering 1 g calcium disodium EDTA intravenously and collecting urine for 24 hr; the collection contained 2.19 μmol (454 μg) lead.

Formal neuropsychological evaluation included the Wechsler Adult Intelligence Scale—Revised, Trailmaking Test, Finger Tapping Test, Grooved Pegboard Test, Boston Naming Test, California Verbal Learning Test, Profile of Mood States, and Recognition Memory Test. These tests were interpreted as showing mild impairment in acquisition of new information. There was some loss of information from visual memory, but retention of verbal information was intact. There was evidence of inconsistency in concentration and of a decline in performance of a visuospatial transcription task, believed by the neuropsychologist not to be attributable to depression. The patient's responses to the Profile of Mood States were not suggestive of a disturbance of affect.

Diagnosis and Treatment

His presenting complaints were attributed to either major depression (DSM-III-R 296.2) or organic mood disorder (i.e., a mood disturbance etiologically related to lead intoxication; DSM-III-R 293.83). A separate diagnosis was neuropsycholog-

ical deficits consistent with chronic lead toxicity. Although his 24-hr urinary excretion of lead following EDTA challenge was below the 2.9 μmol (600 μg) threshold generally considered to indicate an excessive body burden of lead, we believed that his neuropsychological deficits and new-onset depression may have been related to his long-term occupational lead exposure and, therefore, warranted a trial of chelation therapy. On this basis, we offered the patient DMSA chelation, and he accepted.

Concerned about the possibility of DMSA–fluoxetine interaction, we elected, following discussion with the patient and his psychiatrist, to discontinue fluoxetine for several weeks prior to the initiation of DMSA therapy. Immediately prior to commencing DMSA therapy, the patient was examined and reported recurrence of his feelings of depressed mood and anhedonia, and he had a depressed-appearing affect.

DMSA was administered in accordance with McNeil Consumer Products Compassionate Use Protocol 90-09 (McNeil Consumer Products Company, Fort Washington, PA). The patient was removed from work to avoid occupational lead exposure while he was taking the medication, and he was counselled to abstain from any alcoholic beverages while taking DMSA [Dhawan et al., 1989]. He took 800 mg (10 mg/kg) orally three times daily for 5 days, followed by 800 mg twice daily for another 14 days. During this time his blood lead level fell from 1.25 μmol/liter (26 μg/dl) on day 0 to 0.14 μmol/liter (3 μg/dl) on day 7, 0.24 μmol/liter (5 μg/dl) on day 14, and 0.24 μmol/liter (5 μg/dl) on day 21. His 24-hr urinary lead excretion was 0.3 μmol (66 μg) on day 0, 0.96 μmol (198 μg) on day 7, 0.79 μmol (164 μg) on day 14, and 0.06 μmol (12 μg) on day 21. He experienced no adverse effects from the DMSA.

At the completion of DMSA treatment, the patient reported "feeling like his old self again," referring to his improvement in mood, more restful sleep, decrease in fatigue, and greater enjoyment of activities. He also reported substantially less irritability. On examination, his affect appeared brighter. His psychiatrist, after follow-up examination, concluded that antidepressant therapy was no longer indicated. During a telephone follow-up 2 months later, the patient stated "I'm one hundred percent better than when I started," and reported that he had not experienced decline in his mood since treatment.

Efforts were already underway at the plant to improve hygiene and minimize lead exposure; these continued. The patient was returned to his usual job following the end of treatment with instructions to comply carefully with such precautions as handwashing before eating, showering and changing clothes before leaving work, and use of a respirator when necessary. He also received a medical restriction requiring transfer to a nonleaded area of the plant for blood lead levels above 30 μg/dl, the standard practice in our clinic following cases of lead toxicity in workers at continuing risk of exposure.

DISCUSSION

In this moderately lead-exposed patient with symptoms of depression, a dramatic improvement in mood and successful cessation of antidepressant therapy occurred following treatment with the heavy metal chelator DMSA. Four explanations for this improvement are possible. First, it may have been a part of the natural history of this patient's depression. Because depression is a disease characterized by spontaneous remissions, the improvement may have occurred without any intervention. Second, it may have been due to placebo effect. Because this report describes a single

patient, that possibility cannot be excluded. Third, it may have been due to a direct antidepressant effect of DMSA, although no such effect has previously been reported. Fourth, it may have been secondary to a decreased lead level in the patient's central nervous system following DMSA treatment. The first, second, and fourth possibilities can be sorted out definitively only in clinical trials of DMSA in depressed, lead-exposed patients.

Major depression may be difficult (or impossible) to distinguish clinically from organic mood disorder caused by lead toxicity. Lead toxicity may feature loss of appetite [Hammond et al., 1990], fatigue, decreased libido, and depressed mood, all symptoms of depression [Cullen et al., 1983]. Moreover, lead toxicity is not the only possible explanation of these symptoms in a lead-exposed individual; "endogenous" depression may arise in such individuals, just as in those who are unexposed to lead.

One problem with DMSA therapy is cost. The 19-day course we used required 344 10-mg tablets, which would cost over $1,000 at current retail prices [Drug Topics, 1992]. To this must be added the cost of medical monitoring before and during DMSA therapy, and, since workers must be unexposed to lead during chelation therapy, the cost of lost worktime. This brings the cost of a course of therapy to approximately $3,000. Multiple courses of therapy may be needed to effect a significant reduction in body lead burden, increasing costs substantially. This further emphasizes that primary prevention is preferable to treatment of lead toxicity.

Further study is needed to establish the efficacy of DMSA in treating affective disorders in lead-exposed patients. At present, however, chelation should be considered in patients with a history of lead exposure who have even modestly elevated blood lead levels and body burdens (documented with EDTA challenge) and who present with symptoms of depression.

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