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CASE REPORTS

HEMOLYTIC ANEMIA FOLLOWING SUCCIMER ADMINISTRATION IN A GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENT PATIENT

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ABSTRACT

Because of its favorable side effects profile, the oral chelating agent dimercaptosuccinic acid is often used for treatment of lead intoxication. We report a case of a 45-year-old black male with glucose-6-phosphate dehydrogenase deficiency and a 17 year history of occupational lead exposure who developed hemolysis during treatment with dimercaptosuccinic acid for symptomatic lead intoxication. *(Key Words: dimercaptosuccinic acid; hemolytic anemia; lead toxicity; human.)*

INTRODUCTION

The chelating agent dimercaptosuccinic acid (DMSA, succimer) has several potential advantages when compared to the conventional agent used for treatment of lead toxicity, calcium disodium EDTA. DMSA is administered

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orally, while calcium disodium EDTA is administered parenterally, and is reported to have increased efficacy for removing lead from soft tissue and decreased toxicity (1-4). DMSA has been approved by the US Food and Drug Administration for treatment of lead toxicity in children (5).

Reported toxicity from the agent includes elevations of serum liver enzymes, gastrointestinal discomfort, and skin rash (1,5,6). Hemolytic anemia has not been described. We report a case of hemolytic anemia in a man administered DMSA for treatment of lead intoxication.

Case Report

History of Present Illness

The patient was a 45-year-old black male with a 17 year history of exposure to inorganic lead referred for second medical opinion under the OSHA Lead Standard (CFR 1910.1025). The patient reported a ten year history of generalized arthralgias of the shoulders, elbows and knees. He had a five year history of abdominal discomfort associated with diarrhea, food intolerance, and decreasing appetite. He denied weight loss. He experienced frequent headaches and reported a subjective sense of diminished memory which his wife corroborated. He had no past medical history of anemia, renal or neurologic disease, adverse drug reactions, or allergies. He was taking no medications at the time of evaluation.

Social and Occupational History

The patient was a non-consumer of tobacco, alcohol, and controlled substances. He had been employed for 17 years at a lead battery manufacturing facility where he worked in a reclamation area and a casting area. Company records of past blood lead levels were available. During his first three years of employment the patient's blood lead levels ranged from 1.4 - 3.1 μmol/L (30 μg/dL - 65 μg/dL), during the next seven years, his blood lead levels were stable at about 2.4 μmol/L (50 μg/dL); and during the subsequent seven years until examination, his blood lead levels ranged from 1.2 - 1.4 μmol/L (25 μg/dL - 30 μg/dL).

Physical Examination

The patient was a well developed, well nourished male in no distress. At the time of initial examination he weighed 80 kg, had a blood pressure of 134/86 mm Hg, heart rate of 70 bpm, and respiratory rate of 16/min. No gingival "lead line" was noted. On neurological examination the patient was observed to speak slowly but was oriented in three spheres, displayed appropriate affect, and made logical associations. His cranial nerves, sensory function, deep tendon reflexes, motor function, coordination, and balance were all normal.

Routine Laboratory Evaluation

At the time of initial examination the patient had a white blood cell count of 4.1 x 10^6/mm^3 (Normal 4.5 - 11.0 x 10^6/mm^3), a hemoglobin of 14.7 g/dL (Normal 14.0 - 18.0 g/dL) and a hematocrit of 43.3% (Normal 42.0 - 52.0%). The red blood cell mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration were 93.7 fl (Normal 80.0 - 99.9 fl), 31.8 $\mu\mu$g (Normal 27.0 - 31.8 $\mu\mu$g), and 34.0% (Normal 32.0 - 36.9%), respectively. Automated blood chemistry profile including serum proteins, liver enzymes, renal function tests, and electrolytes was entirely normal. The patient's blood lead level was 1.3 μmol/L (27 μg/dL), suggestive of increased absorption of lead.

Special Diagnostic Testing

Full neurobehavioral evaluation, performed to document objectively the patient's complaints of altered cognitive function, showed impaired attention, impaired motor abilities, dysnomia, and inconsistency in memory for new information.

A diagnostic chelation challenge was performed by measuring the 24 h urinary excretion of lead after administering 1 g of calcium disodium EDTA by slow IV infusion. The patient excreted 3.4 μmol/24 h (706 μg/24 h) lead. Excretion above 2.9 μmol/24 h (600 μg/24 h) is considered evidence of elevated body burden of lead (7) and lead toxicity was diagnosed.

Treatment and Clinical Course

The oral chelating agent, dimercaptosuccinic acid, was administered for treatment of lead toxicity. The patient took 800 mg (10 mg/kg body weight) orally three times daily for five days and was instructed to take 800 mg twice daily for the remainder of treatment. He was removed from lead exposure while taking the medication and counselled to abstain from consumption of alcoholic beverages during treatment (8). On the day prior to treatment (Day 0), protocol laboratory testing consisting of CBC with differential, automated chemistry profile, urinalysis, and blood lead level was obtained. In addition, laboratory evaluation was performed weekly (Table 1). The hemoglobin and hematocrit dropped from 15.0 g/dL and 43.5% on the day prior to treatment to 11.7 g/dL and 34.1% on day 07. Total bilirubin increased from 0.8 mg/dL on the day prior to treatment to 2.5 mg/dL on day 07. The patient was contacted on day 08 and instructed to discontinue treatment. At that time he reported fatigue but no other symptoms. Repeat hematologic studies showed a gradual increase in the hemoglobin and hematocrit with normalization of the bilirubin. The blood lead level decreased from 1.4 μmol/L (30 μg/dL) on the day prior to commencement of treatment to .05 μmol/L (1 μg/dL) on day 07 of treatment.

TABLE 1

Selected Laboratory Results

Laboratory Tests	Day 0	Day 07	Day 14	Day 21	Day 215
WBC ($1000/mm^3$)	3.7	6.4	3.4	2.8	3.6
Hemoglobin (g/dL)	15.0	11.7	12.6	13.5	13.7
Hematocrit (%)	43.5	34.1	36.6	38.9	41.7
Tot. bilirubin (mg/dL)	0.8	2.5	0.3	0.5	0.8
AST (SGOT) (U/L)	20	32	20	25	32
Retic count (%)	---	---	1.9	0.9	---
Blood lead (μg/dL)	30	1	7	10	18

The glucose-6-phosphate dehydrogenase (G6PD) level was measured seven months after discontinuation of DMSA and was found to be 38 $U/10^{12}$ RBC (Normal 146 - 376). G6PD levels measured during and immediately following hemolysis are likely to result in false increases. Hemoglobin and hematocrit were 13.7 g/dL and 41.7%, serum bilirubin was 0.8 mg/dL and the blood lead level was 18 μg/dL. In an effort to identify hemoglobinopathies characterized by unstable hemoglobin, a hemoglobin electrophoresis was performed. The phoresis phenotype was AA. Hemoglobin F accounted for less than 2% of the sample, and hemoglobins S and C were not detected. The conclusion of the testing laboratory was that no elevations in abnormal hemoglobin concentration were detected and that additional hemoglobin stability tests were not indicated.

DISCUSSION

G6PD deficiency is a group of X-linked genetic defects that have in common a gene mutation at the G6PD enzyme locus (9). More than 300 polymorphic variants have been described (10). Although uncommon among white individuals, it is found in 11-20% of African-Americans in the US

(10,11). The majority of G6PD deficient individuals have normal hemoglobin levels and normal or near normal red blood cell life spans. However, the condition has been associated with shortened red blood cell life span manifest as hemolytic anemia under oxidative stresses, the most common of which are infection, drugs such as antimalarials, sulfa drugs, and nitrofurantoin, and exposure to specific chemicals such as trinitrotoluene and naphthalene (12). The biomolecular pathology is believed to be inadequate reduction of intracellular peroxides (13).

Anemia following DMSA administration for lead toxicity in G6PD deficient individuals is potentially the result of three distinct pathological processes. The first is hemolysis caused by the drug itself in these patients. The second is underlying hemolysis that may occur as a direct result of lead toxicity (14). The third is an impaired capacity to compensate with active hematopoiesis, one of the early and typical manifestations of lead toxicity (15). Therefore, DMSA-induced hemolytic anemia could be a more serious problem for lead intoxicated patients than in other clinical settings.

Hemolytic anemia in G6PD deficient patients who take DMSA may depend on several factors: the size of the G6PD deficient population who take the drug, the incidence of hemolytic anemia among them, and possible genetic differences in the activation of DMSA to the mixed disulfide, *L*-cysteine-DMSA.

The population that may take DMSA is sizeable. The Agency for Toxic Substances and Disease Registry estimates over 3 million children in the US have blood lead levels in excess of 15 μg/dL (16), and the National Institute for Occupational Safety and Health estimates that 1.4 million adult workers in the US are potentially exposed to lead (17). In both groups, African Americans are over-represented (16,18,19). Occupational and environmental exposures to lead in developing nations are excessive and poorly controlled (20-22). Regions of the developing world where G6PD deficiency is common, including Mexico and Africa, are likely to contain many persons who may be candidates for DMSA treatment.

The risk of hemolytic anemia for G6PD deficient persons who take DMSA is unknown. Graziano *et al.* (23) reported administration of DMSA to two G6PD deficient lead intoxicated children who tolerated the treatment without evidence of hemolysis. Despite increasing clinical use of DMSA, this reaction has not been previously reported, suggesting that it may not be a common complication among patients with G6PD deficiency.

In the absence of a typical reticulocytosis other causes were considered. No hemoglobin abnormalities were detectable on hemoglobin electrophoresis. Since G6PD deficiency has many polymorphic variants and genetic differences in the metabolism of DMSA are only recently under investigation, further experience with DMSA in G6PD is needed.

Other possible explanations for the patient's hemolysis include surreptitious use of other medications or an overdose of DMSA, suggested by the sharp decrease in blood lead. We have observed a similar decrease in blood lead level on day 07 of treatment among workers with a similar exposure history. The urine DMSA:DMSA-cysteine, an index of activation and a correlate of lead excretion, was not measured.

This case raises the question of whether G6PD levels should be obtained before DMSA treatment. On a population basis, the cost of such testing could be considerable and cost-benefit ratio is unknown. Information about the incidence and severity of anemia following treatment are needed before rational recommendations are made.

Whether or not prior testing for G6PD deficiency is performed, a complete blood count no later than day 07 continues to be an essential component of DMSA therapy.

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