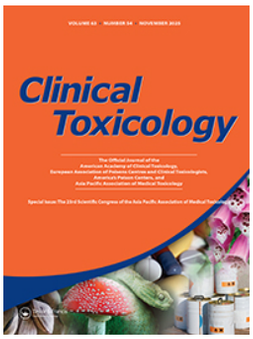

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ARTICLES

Safety and Efficacy of Meso-2,3-dimercaptosuccinic Acid (DMSA) in Children with Elevated Blood Lead Concentrations

J. Julian Chisolm, Jr.

Lead Poisoning Program, The Kennedy Krieger Institute, Baltimore, Maryland

ABSTRACT

Objective: To evaluate the safety and efficacy of meso-2,3-dimercaptosuccinic acid in the treatment of children with lead toxicity. Design: This was an open-label study in 59 children 12–65-months old, with pretreatment whole-blood lead levels of 25–66 μg/dL, who received 116, 26–28 day courses of oral dimercaptosuccinic acid, while residing either in the Pediatric Clinical Research Unit of the Johns Hopkins Hospital or in lead-safe housing during the outpatient portion of the study. Results: All, who completed the study, showed sharp decreases in blood lead concentration during therapy, but 2–3 weeks following completion of drug therapy, blood lead concentration rebounded to an average of 58% (23 μg Pb/dL of whole blood) of their average pretreatment blood lead concentration (40 μg Pb/dL of whole blood). There were no adverse reactions attributable to dimercaptosuccinic acid; however, 2 of the 59 patients were reexposed to defective lead paint and experienced sharp increases in blood lead concentration while on therapy. In one instance, the child's blood lead concentration increased from 20 to 90 μg Pb/dL whole blood in 1 week. Other unexpected events were discussed in the text. Conclusions: Dimercaptosuccinic acid is apparently safe and does mobilize lead into the urine, but not the essential metals, zinc and copper. Reexposure is always a danger; therefore, all children, while on therapy, should be monitored for their blood lead concentration at

Correspondence: Dr. J. Julian Chisolm, Jr., Kennedy Krieger Institute, 707 N. Broadway, Baltimore, MD 21205. Tel: 410/502-9081; Fax: 410/502–8190.

weekly intervals during and immediately after therapy. No conclusions can be drawn from this study regarding long-term beneficial effects, if any, of this drug on late neurocognitive outcome.

INTRODUCTION

Meso-2,3-dimercaptosuccinic acid (DMSA, succimer) is the first orally effective and relatively nontoxic chelating agent for the treatment of increased lead absorption and lead poisoning. On the basis of experimental data and a few human case reports, DMSA is also effective in arsenic (including combined arsenic and lead poisoning[1]) and mercury (including methyl mercury) poisoning. The topic has been extensively reviewed by Aposhian in 1983,[2] 1990,[3] and 1995[4] and Angle, 1993.[5] The active complex that binds lead is a DMSA-cysteine disulfide with lead being bound between one thiol group and a carboxyl group. Asiedu *et al*.[6] has presented evidence that there is enterohepatic recycling of DMSA. In primates the amount absorbed and eventually appearing in urine is approximately 18–20%.[6,7]

The use of DMSA was first reported in 1954 as an antimony DMSA complex for the treatment of schistosomiasis.[8] The first report of DMSA's use in the treatment of occupational lead poisoning was from China in 1965.[9] In the United States the first clinical use was reported by Graziano *et al*. in adults in 1985[10] and in children in 1988.[11] Domingo *et al*.[12] have shown that DMSA administered to pregnant mice, in relatively low doses, resulted in developmental toxicity including stunting of growth in both mother and fetus and increased fetal wastage. Therefore, it is strongly recommended that this drug not be given to pregnant women.

The objective of this project was to evaluate the safety and efficacy of DMSA in the treatment of children with elevated blood lead concentrations. These studies were previously reported in part.[13]

MATERIALS AND METHODS

Clinical Material

The 59 subjects (31 females, 28 males) of these studies who received a total of 116 courses of DMSA were drawn from the Kennedy-Krieger Institute's Outpatient Lead Clinic.

Prior to the start of this study, exclusion of children with glucose-6-phosphate dehydrogenase (G6PD) deficiency and sickle cell disease was seriously considered, but was not done when studies elsewhere indicated that these patients were taking DMSA without incident.

This was an open-label convenience study.

Inclusion criteria were as follows:

1. Male or female child 12–72 months of age. (Actual range: 12–65 months of age.)
2. Patients with pretreatment blood lead concentration (PbB) in a range of 25–120 μg Pb/dL of whole blood. (Actual PbB range in children studied was 25–70 μg Pb/dL.)
3. Patients with ''lead-safe'' housing in which they may stay while receiving DMSA as outpatients.
4. Parent or legal guardian has signed written informed consent.

During the course of this study, the Kennedy Krieger Institute operated a Safety House without lead hazards for children with lead poisoning. Ten of the 59 children in this study were housed during treatment in this facility adjacent to the main building, where DMSA was given by the staff.

Exclusion criteria were as follows:

1. Patients with known hypersensitivity to similar chemical chelating agents or drugs.
2. Patients with a history or current findings of serious cardiovascular, renal, endocrine, metabolic respiratory, dermatologic, or gastrointestinal disease not consistent with lead toxicity.
3. Patients with symptoms of lead encephalopathy who are vomiting or unconscious and therefore unable to swallow and/or retain the drug.
4. Patients who have received any investigational drug during the preceding month. We extended this to include calcium disodium ethylene diaminetetraacetate ($CaNa_2$ EDTA) within the previous 2 months. For DMSA the exclusionary waiting period between courses was 2 weeks. None of the children enrolled in this study was symptomatic.

The critical factor to determine whether a child could be admitted to the study was the availability of lead-safe housing, in which they could receive DMSA as outpatients. If this could not be obtained, they were not admitted to the study. For the purposes of this study, ''lead-safe'' housing included the Kennedy Krieger Institute's

Safety House, a completely rehabilitated 150-year-old mansion, adjacent to the Institute. Frequent dust lead tests were carried out in the house to determine that the dust lead levels were within acceptable range. Other houses included in this category were newly built housing on the periphery of the city in which lead paints have not been used, gut-rehabilitated housing in the inner city, and public housing in which, by long tradition in this city, lead paint had not been used. Such homes were either the homes of grandmothers or other relatives who would agree to take the child while on therapy. The Institute also had a second gut-rehabilitated ''lead-safe'' house where patients not on therapy could await the availability of lead-safe housing in the community. It was a purpose of this study to determine what could be accomplished under the best environmental conditions. Blood lead levels were monitored at weekly intervals, with the result being available within 30 minutes while the child was at the clinic so that any unexpected exposure could be identified immediately.

Protocol

The initial pilot protocol called for the administration of DMSA 1050 mg/m^2/d in 3 divided doses for the first 5 days of treatment, after which DMSA was reduced to 350 mg/m^2/d in 2 divided doses during days 6–10. This protocol was administered to 4 patients only, because it became evident that in 2 of the 5 courses, PbB increased between days 6–10 on the lower dose of the drug (Figure 1), while these patients were at the Pediatric Clinical Research Unit (PCRU) of the Johns Hopkins Hospital. There was no question of their ingesting additional lead as they were not outside of the research unit. We then changed to what became the basic protocol for the remainder of the studies.

Table 1 shows the demographic data and Table 2 shows the inpatient/outpatient treatment protocol. The children in this group actually received the drug for 26 days. Two days were given over to pretreatment acclimatization and control data in the PCRU. The protocol for

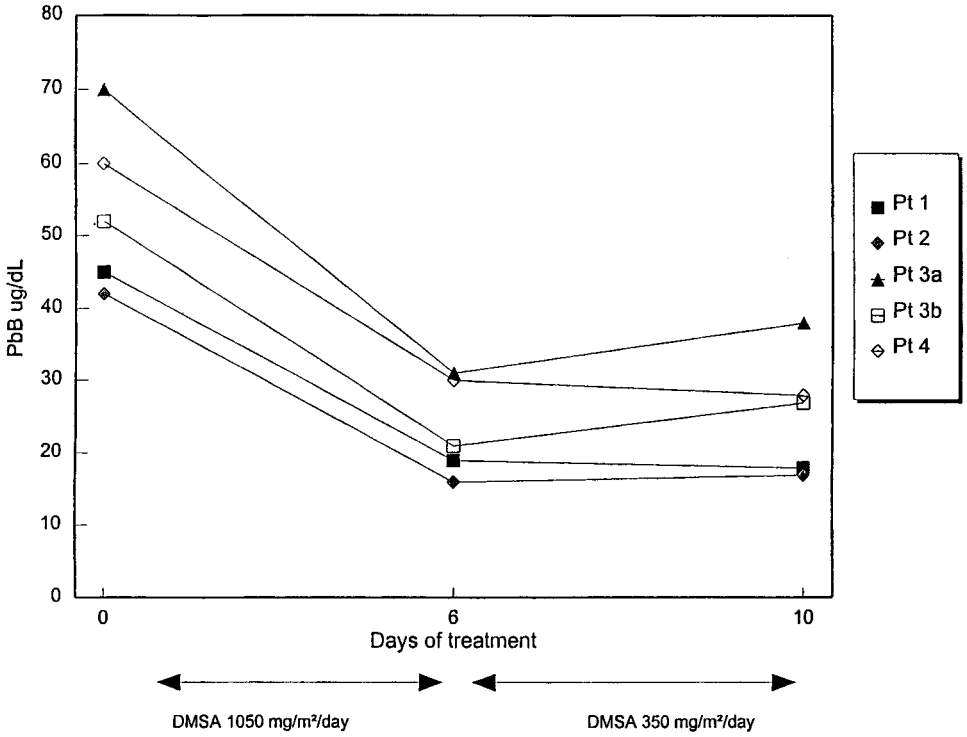

Figure 1. Changes in blood lead concentration (PbB) during 10-day pilot course of therapy with meso-2,3-dimercaptosuccininc acid (DMSA). Patients in PCRU received DMSA 1050 mg/m^2/day for 5 days immediately followed by DMSA 350 mg/m^2/d for next 5 days. Note that patient 3, a heavily leaded child with initial PbB of 70 μg/dL, rebounded while on therapy when dosage was reduced. 3a and 3b show first and second courses in patient. The other 3 patients showed either no change or slight decrease in PbB when dosage was reduced. In 2 of the 3, initial PbB were less than 50 μg/dL, as shown in figure.

Table 1

*Demographic Data***

Protocol Total No. of Courses/Patients*				
Outpatient	75/42			
In/Outpatient	41/17			
Total No. of Patients	Female	Male	Caucasian	African-American
59	31	28	8	51
G6PD deficient homozygous		5		
heterozygous	1			
Sickle Cell Disease				1
Age range in months:	Avg	Min	Max	
	35	12	65	
PbB (μg/dL)	Avg	Min	Max	
Before the first course of therapy	41	24	66	

*Number of courses of therapy exceeds number of patients, since most patients received multiple courses.

**Does not include patients of pilot study (see Figure 1).

the outpatient protocol differs only in that there were no 24-hour collections of urine. These protocols were instituted and approved by the Food and Drug Administration (FDA) before the drug was released in January 1991. When released, a treatment course of 21 days was recommended by the FDA; however, this protocol was continued throughout these studies, which were done between 1988 and 1992. In general, they were enrolled in the clinic on a Wednesday. If the child was toilet trained, and a bed was available, the child was admitted to PCRU 2 days later. Otherwise, the child was enrolled in the outpatient protocol and came back after 2 days to make sure that there was no laboratory finding that would disqualify the child for the study. Those on the inpatient/outpatient protocol, when discharged, were sent either to a lead-safe home or to the Kennedy Krieger Institute's Lead-Safety House to complete an additional 21 days of therapy, whereas those on the outpatient protocol would have received all 28 days of their therapy at this location or in some other ''lead-safe'' housing. Five of the patients had been previously treated with $CaNa_2$ EDTA, with their last treatment occurring at least 2 years, 2 years, 2 years, 4 months, and 2 months, respectively, prior to enrollment in this DMSA study. These 5 patients, who had shown rather stable PbBs, in the range of 35–45 μg/dL during the interval could not be enrolled in the DMSA study until they had been relocated to a lead-safe housing in the community or the Kennedy Institute's Lead Safety House. In these protocols, all children received DMSA 1050 mg/m^2/d in 3 oral doses for the first 5 days, at which point the dosage was reduced to 700 mg/m^2/d and divided into 2 doses over the next 21–23 days. No increases in PbB during therapy (except in 2 cases of reexposure) occurred on this standard basic protocol which included 8 children with initial PbB≥50 μg/dL. Because DMSA is only provided in 100-mg capsules, actual doses were rounded to the nearest 100 mg and mixed in fruit juice just prior to administration. Serum chemistries included serum-urea nitrogen, glucose, calcium, phosphorus, bilirubin, creatinine, uric acid, albumin, cholesterol, alanine transferase (ALT), aspartate transferase (AST), and alkaline phosphatase activity. Blood counts included hemoglobin (Hb), hematocrit (Hct), erythrocytes, mean corpuscular volume (MCV) and red cell indices, platelets, and white blood cells with differential count. Compliance in each course was judged by the keeping of appointments and weekly pill counts. Also a history was obtained to ensure the child was still remaining in the ''lead-safe'' house. Compliance was judged as excellent if all therapy was taken and all visits were kept (52 courses, 37 patients); compliance was judged as good (18 courses, 13 patients) if all therapy was taken and only the fourth follow-up visit was missed and at least 1 follow-up visit was kept; compliance was judged as fair, (12 courses, 9 patients) if one follow-up visit was missed and the third-week appointment was missed, which meant the child would not get the full therapeutic course. The child's compliance was judged as poor or incomplete

Table 2

Flow Chart: Basic Inpatient/Outpatient Treatment Protocol

Study Day#	Days	ECG	PbB	M12	G6PD, Hemoglobin Typing	FEP	Blood ALAD	Count	Urinalysis	24-hr Urine Collection
0	Clinic Visit		+	+		+	+	+	+	
1	Admit to PCRU	+	+		+	+			+	
2	Control day 1									+
3	Control day 2									+
4	Inpatient treatment day 1		+	+		+	+	+	+	+
5	Inpatient treatment day 2									+
6	Inpatient treatment day 4								+	+
7	Inpatient treatment day 4									+
8	Inpatient treatment day 5	+	+	+		+	+	+	+	+
13	Outpatient treatment day 10		+	+		+	+	+	+	
20	Outpatient treatment day 17		+	+		+	+	+	+	
27	Outpatient treatment day 24		+	+		+	+	+	+	
34	Follow-up clinic visit		+	a		+	+	+	+	
41	Follow-up clinic visit		+	a		+	+	+	+	

a = if abnormal during treatment; M12 = serum chemistries, see text for detail; G6PD = glucose-6-phosphate dehydrogenase activity; FEP = free erythrocyte protoporphyrin; ALAD = aminolevulinic acid dehydrogenase activity; Blood Count = complete blood count; Urinanalysis = including microscopic.

if a number of appointments were missed, if not all medications were taken, or if the patient simply failed to return after being discharged into the outpatient department. There were 32 attempted courses in this last group. Two patients were disqualified because of reexposure to lead against instructions. A child's compliance might vary from one course to another, usually for social reasons, so that compliance was determined separately for each course.

Laboratory Methods

Blood was collected for lead and other serum chemistries using stainless steel needles with polypropylene shanks and Starstedt (polypropylene) Monovet® serum and ammonium heparin syringes. The serum chemistries, complete blood counts, urine analyses, hemoglobin electrophoresis, and G6PD quantitative assays with simultaneous reticulocyte counts were measured in the clinical laboratories of the Johns Hopkins Hospital. All other measurements were made in the Trace Metals Laboratory.

Urine was measured throughout for zinc (ZnU) and copper (CuU) by flame atomic absorption spectrophotometry (FAAS) and lead (PbU) by graphite furnace AAS (GFAAS). The method of standard addition was used. Lead in blood was measured in duplicate (SD ± 1.2 μg/dL) by anodic stripping voltametry (ASV) because PbB results were available within half an hour, so that patients could be monitored according to current blood lead values. Primary standardization was with biologically bound

lead in human blood as determined by thermal ionization mass spectroscopy (TIMS). As shown elsewhere,[14] ASV provided results with equivalent accuracy but slightly less precision than GFAAS. The laboratory serves as a reference laboratory for the blind interlaboratory proficiency programs in PbB for the State of New York and Wisconsin State Laboratory of Hygiene, Wisconsin. (Special precautions are necessary when blood lead is measured by ASV in patients on DMSA since DMSA has a high affinity from mercury, and therefore, can poison the electrode. All samples for blood lead were drawn in the early morning at least 10 hours after the last dose of DMSA, and before the first dose of DMSA in the morning. A minimum period of 8 hours was used in one part of the study. This approach was verified by paired determinations by ASV and GFAAS. ASV is satisfactory for K_3EDTA anticoagulated blood, provided the collection tube is at least half full of blood and the reagent contains nickel).

ALAD (porphobilinogen synthase, PBG-S) activity was measured by the method of Chisolm, Thomas, and Hamill.[15] Specimens for PBG-S were immediately stored at −70°C in 1.5-mL polypropylene tubes with captive plugs prior to the analysis. Serum ceruloplasmin was measured by the method of Ravin,[16] and DMSA and cysteine in urine were measured by the method of Maiorino *et al*.[17] These samples were processed within 15 minutes. All labware was cleaned with Acationox®, soaked in 10% nitric acid, and rinsed in distilled-deionized water. Statistical analysis was carried out primarily by least squares regression analysis.

In the outpatient portion of the protocol, the child was always given a one week's supply of medication with a few extra capsules and therefore had to return each week to get a new supply.

In the inpatient/outpatient protocol, electrocardiograms (ECGs) were obtained just prior to the start of therapy and after 4 days of therapy. Serum ceruloplasmin was obtained because it was anticipated that the drug might mobilize copper. This turned out not to be the case. Urinary copper values scarcely increased above baseline during therapy in 15 children and their ECGs showed no change during the first 4 days of therapy. All ceruloplasmin values remained within the normal range for the age of the child, with one exception—a child with iron deficiency anemia, who had two borderline low values with the other 6 being within the normal range. Therefore, the above mentioned measurements of ceruloplasmin and urinary copper were stopped after the first 15 patients once the urinary data made it clear that copper was not being mobilized by DMSA.

RESULTS

The 59 patients received a total of 116 courses of DMSA. Figure 2 shows (mean±2 SD) changes in blood lead concentration before, during, and after therapy in patients whose compliance was judged as either excellent or good (66 courses of therapy). Because no difference was found between the outpatient and inpatient/outpatient protocols, the data were combined. Because no difference was found in PbB during therapy in patients who were treated in the Safety House or a lead-safe home, these data were also combined. Virtually all the decrease of PbB occurred during the first 5 days of therapy. When the dosage was reduced to 700 mg/m^2/d, the lower PbB level was maintained or perhaps lowered slightly.

Average PbB after therapy rebounded to 23 μg Pb/dL or 58% of the average pretreatment value. Further follow-up indicated the peak of rebound PbB occurred about 6 weeks after therapy and stabilized thereafter, probably as a result of internal redistribution of lead from bone to soft tissue, including blood. ALAD activity was inversely related to PbB and therefore mirrored the change in PbB.

The amount of lead removed was calculated from the circulating blood in comparison with the amount actually excreted in the urine during the first 8 hours of therapy. Blood volume was assumed to be 80 mL/kg of body weight. Table 3 shows representative data from 12 patients admitted to the PCRU. In each instance the amount of lead excreted from urine during the first 8 hours exceeded the estimated amount that would be removed from the blood pool, assuming that all of the lead came, in fact, from the blood pool. No statistically significant relationship was found in regression between PbB and the amount of lead excreted in 8 hours, 24 hours ($R^2 = 0.10$), and 5 days.

Six patients who had been admitted to the PCRU were brought back at weekly intervals for 6-hour urine collections. Nine studies were carried out in these 6 patients. Blood lead concentration was maintained during the outpatient phase on average at a level below 20 μg Pb/dL. Even so, the urine lead/creatinine ratios in the 6-hour collections indicate that a substantial diuresis of lead still occurred in comparison with the pre- and posttreatment ratios (Table 4).

In 7 other patients, fractional collections of urine were obtained to measure urinary lead, zinc and copper, urinary DMSA, and cysteine during the first 6–8 hours after the initial dose of DMSA. A representative example is shown in Figure 3. After DMSA was administered, there was a marked increase in the urinary output of cysteine.

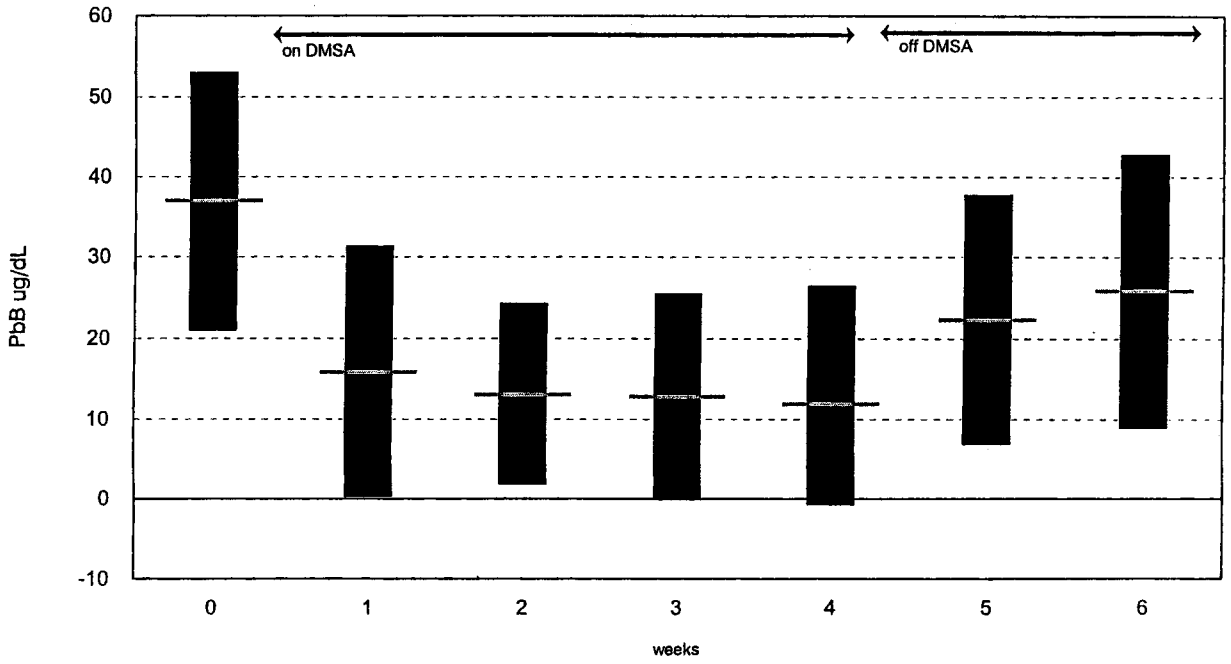

Figure 2. PbB changes before, during, and after DMSA therapy. Bar graph indicates ±2 SD in 66 courses of therapy in 39 patients. These data are drawn from patients, classified as showing excellent and good compliance.

Table 3

Estimated Amount of Lead Removed from Circulating Blood Pool in Comparison with Total Amount of Lead Excreted in Urine During First 8 Hours of Treatment with DMSA

Patient No.	Blood Lead µg/L Pretreatment (A) After 8 hours (B)		Est. Pb Removed* from Blood Pool		Total Urine Pb Output (µg Pb Post 1st 8 hours)	Total Urine Pb Output/Body Weight (µg/kg)
	A	B	A–B	µg Pb		
1	340	265	75	128	263	12
2	420	350	70	103	245	13
3	315	250	65	85	144	9
4	355	270	85	99	815	55
5	380	340	40	50	284	18
6	560	505	55	78	491	28
7	355	300	55	66	234	16
8	370	310	60	73	198	13
9	410	350	60	77	211	13
10	415	360	55	62	330	24
11	345	310	35	54	116	6
12	320	260	60	70	131	9

*Assume blood volume = 80 mL/kg of body weight.
Estimated amount of lead removed from blood pool—decrease in blood Pb(A–B)x estimated blood volume.

Table 4

Ratio of Urinary Outputs of Lead and Creatinine Before, During, and After Outpatient Treatment

Before Treatment 24 hour Collection	Outpatient Treatment 6–8 hour Collection	Posttreatment 6–8 hour Collection
0.18	0.59	0.03
0.10	0.45	0.14
0.11	0.34	0.02
0.08	1.14	0.13
0.16	1.12	0.10
0.12	0.42	0.02
0.32	2.96	0.28
0.32	3.14	0.14
0.30	1.04	0.17

$$\text{Ratio} = \frac{\text{PbU } \mu\text{g/sample}}{\text{Creatinine mg/sample}}$$

Urinary lead generally peaked during the second or third hour after the administration of the drug. Copper showed either no increase or modest increase during the second or third hour; zinc reacted in a similar fashion. The output of lead in urine increased dramatically by six- to tenfold. These data are in agreement with the data of Aposhian[3] and Graziano *et al*.[11]

The output of lead, zinc, and copper in urine during the first 5 days of DMSA indicated that there was no substantial increase in the output of copper and that the urinary output of zinc during therapy did increase perhaps twofold to an average of 530 mg/d, a value still within the acceptable range for young children.

The patients with G6PD deficiency and sickle cell disease (Table 1) tolerated DMSA well without incident.

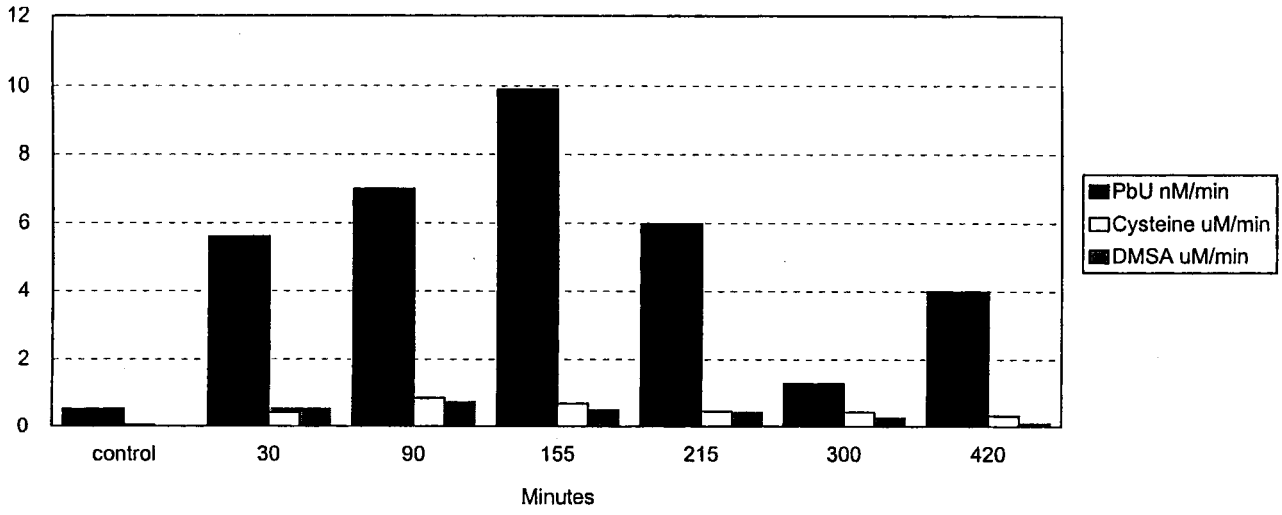

Figure 3. Rate of excretion in urine of lead, DMSA, and cysteine after initial oral dose of DMSA. Note that the excretion of lead is indicated in nanomoles (nM/min), while the much larger excretion of cysteine and DMSA are shown in micromoles (μM/min). Note that lead excretion peaks during the third hour in this patient, and that there appears to be a spike in lead excretion at the end, between the seventh and eighth hour during the child's supper. This observation led Asiedu *et al*.[6] to pursue it further with regard to enterohepatic recirculation of DMSA. Percent of the dose of DMSA recovered in urine during the 8 hours was 11.5%, which is representative of the 7 patients with whom these studies were made.

Adverse Events

Throughout, every effort was made to relocate children into essentially lead-safe houses. In 2 of the 59 children, we were unable to avoid reexposure during the therapy. These 2 children were not included in the statistics on PbB in as much as they were judged to be noncompliant and the purpose of the study was to determine the effectiveness of the drug under good environmental circumstances. In one patient, the child was admitted to PCRU with a blood lead of 50 μg Pb/dL and discharged from PCRU after 5 days of DMSA therapy with a blood lead of 19 μg Pb/dL. This was maintained for 1 week; however, the following week the child showed up with a venous blood lead concentration of 90 μg Pb/dL whole blood. Against our instructions the child had been taken back from the public housing unit in which she was residing to the old dilapidated dwelling where she first got lead poisoning. She was readmitted and promptly responded to treatment, this time with $CaNa_2$ EDTA. In the other child, while being treated in a rehabilitated home, PbB increased from 14 μg Pb/dL to 45 μg Pb/dL of whole blood during the second week of therapy. The mother was allowing this child to play on the porch while paint was being scraped off an adjacent old house that fell onto the porch. The mother was then instructed to keep the child inside of the house, which she did, and to continue the medication. Under these conditions the child's blood lead concentration decreased during the following week to 28 μg Pb/dL.

Interesting Events

During this study 2 children were identified with rising serum alkaline phosphatase activities. In one child, the drug was stopped and since his blood lead concentration remained below 25 μg/dL, he was not rechallenged. In the other child, during the second course of DMSA, serum alkaline phosphatase increased and reached a peak of 1707 IU/L while the drug was continued. Alkaline phosphatase activity decreased during the last week of the second course of therapy. About 2 months later the child received the third course of oral DMSA and about 1 month after that a fourth course of oral DMSA. All serial alkaline phosphatase activities remained within normal limits during these 2 courses. Fractionation of the serum indicated that the alkaline phosphatase was derived primarily from the bone, not liver (gamma glutamyl transferase remained normal). This falls within the little known category of benign transient hyperphosphatasemia,[18] a disorder not associated with any symptoms or other known untoward findings.

No adverse clinical effects have been observed in this or other children subsequently seen in this clinic with a similar phenomenon.

In 15 patients, ceruloplasmin was measured. In all but 1 child, the values remained within normal limits for the age of the child (30–65 mg/dL; age 1–12 years). All but 2 of 8 serial ceruloplasmin measurements remained within the normal range. These 2 dropped to a borderline low level at 26 mg/dL. Ceruloplasmin was found to be within normal levels, even though the drug was continued. The 51-month-old child had iron deficiency anemia. At the time of first admission, HGB 8.8 g, HCT 29.2, MCV 64.7, R/DW 15.75, and serum ferritin 8 ng/mL were all indicative of iron deficiency anemia. The child was placed on ferrous sulfate, given at a different time from DMSA. Four weeks later, hemoglobin had increased to 11.1 g, Hct to 35.5, and MCV to 70.4. Copper deficiency was also found in patients with nutritional iron deficiency anemia.

In one child, therapy with DMSA was started when the eosinophil count was 1%. Ten days later, it increased to 25% of 12,100 leukocytes. The drug was stopped but the child was followed. The eosinophil count decreased from 25% to 4% of 11,500 leukocytes 10 days later. The child was challenged 1 week later at which time the eosinophil count was 2% , where it remained throughout the second full 28-day course of DMSA. Extensive testing revealed no alternate cause for the child's eosinophilia.

Finally, one patient is of particular interest. This boy was admitted to PCRU on a Friday for the control period. At that time the serum transaminases were within the normal range. On Monday morning, 3 days later, just prior to starting DMSA, serum chemistries revealed that serum transaminases had risen to approximately 100 IU/L. This was checked and verified. No further medication was given after the first day. The mother was not compliant with follow-up, so he was not seen again for about a month, at which time serum chemistries were all within normal limits.

DISCUSSION

Blood lead concentration decreased temporarily to less than 35% of the pretreatment value at the very end of the approximately 4-week course of therapy, but rebounded within 2–3 weeks to a value of 23 μg Pb/dL or 58% of the pretreatment value. This is in agreement with the data of Graziano[11] and others[5] who have reported data from children receiving DMSA. Note further in Figure 2 the wide variation in the spread (±2 SD) of responses. Among the children studied, the initial drop in PbB was

clearly associated with an increase in PbU. There was no constant ratio between the amount of lead estimated to be removed from the blood pool and the actual amount found in the urine. These data are compatible with the hypothesis that lead is removed from the soft tissues and rapidly transferred through the blood into the urine. It is also possible that the excess may in large part represent lead removed directly from the kidney, an organ in which lead is known to accumulate. In an attempt to see whether a DMSA lead mobilization test would be of value, we plotted the relationship between blood lead and urinary lead output during the first 8, 24, and 120 hours and found no significant relationships. This confirms the finding of Lee *et al*.[19] in adult lead workers, who also found that PbB was not predictive of the response to DMSA. They did, however, find a statistically significant relationship between urinary lead output and urinary delta-aminolevulinic acid output (ALAU). ALAU was not measured in this study, which involved children with PbB in a somewhat lower range than that found in the lead workers. If Lee *et al*.[19] primed the worker with $CaNa_2$ EDTA just before DMSA, a relationship between PbB and urinary Pb following DMSA was found.

Urinary lead output was markedly increased, whereas the excretions of essential metals, such as zinc and copper, were not increased. This confirms the findings of Graziano *et al*.[11] in children. These data should be confirmed because they provide the basis for suggesting that administration of DMSA may continue to produce a diuresis of lead even when PbB has decreased substantially. Most recently, Woolard *et al*.[20] reported that the excretion of the essential metals, zinc and copper, is not increased in primates. We were particularly careful about copper, in view of our previous experience indicating that 2-3-dimercapto-propane-1-sulfonate (DMPS) was associated with a dose-dependent increase in the excretion of copper but not zinc.[21] To this end we measured, at the beginning of the study, ECGs in 12 patients and found no change during the first 4 days of therapy. We measured urinary copper output in 15 patients, and again found no elevations.

We found no significant changes in 14 of 15 patients in serum ceruloplasmin and only a transient mild depression in one, which normalized during continued therapy. Patients with concurrent iron deficiency anemia may be treated with a therapeutic amount of iron, provided that the iron is given at a different time of day than DMSA. It might also be prudent to give prophylactic amounts of zinc and copper to such patients, because they may be deficient in these metals and iron.

Studies were carried out in 7 patients in whom DMSA and cysteine in urine were measured during the first 6–8 hours after the initial dose of DMSA. Figure 3 shows a typical example. In general, approximately 11% of the administered dose was recovered in the urine during the first 6–8 hours. Studies elsewhere would suggest that the full excretion of a dose of DMSA may require up to 48 hours. Asiedu *et al*.[6] has also reported a series of studies that support the hypothesis that there is an enterohepatitic recirculation of DMSA. This was not measured in this study. Graziano *et al*.[11] also reported a wide variation in the amount of DMSA recovered from the urine. The data are also compatible with the experimental data reported by Aposhian *et al*.,[3,4] indicating that lead is held in a 5-membered heterocyclic ring between the carboxyl group and a thiol of DMSA. This is consistent with the known propensity of lead to bind to sulfur with relatively equal facility on the one hand and oxygen and nitrogen on the other.[22]

Two out of the 59 patients did show increases in PbB during therapy while at home. In both cases, these children were reexposed to lead in deteriorated paint. In one child, the PbB increased during the 1-week period, from 20 to 90 μg PbB/dL. This is an unusually large increment. The increase in PbB probably relates to the sharp increase in exposure and continued abnormal ingestion of lead by this child with voracious pica. Whether DMSA enhanced the absorption of lead in this child with voracious pica is not known. The child had shown normal responses to DMSA when not overexposed to lead. This adds further importance to weekly follow-ups for outpatients—not only to check for compliance in drug administration, but also to check for continued, excessive ingestion of lead. Neither the fixed drug eruptions[23] nor other clearly drug-related adverse reactions were encountered in this study.[24]

CONCLUSIONS

It is clear that DMSA is effective in producing a diuresis of lead, albeit temporary. There have been no serious side effects of DMSA during 116 courses in these 59 young patients. Children with marginal nutrition and those with iron deficiency anemia can be treated with iron provided that the drugs are given at different times. In the course of this study, the main method of finding lead-safe housing for the patients was to relocate them. If patients are to be treated on an outpatient basis, their dwellings should be inspected and professionally cleaned including a high-efficiency particle accumulator vacuum step. A visual inspection will suffice to identify scaling paint; however, samples must be tested for lead in dust. The data indicate that children on DMSA should be checked at least at weekly intervals, both for compliance

and for blood lead response in order to identify a rise in PbB as soon as possible. In our clinic they were brought in and had their blood drawn before they received their morning dose. Whether DMSA will be shown to have any long-term beneficial effect on the neuro-behavioral sequelae of early lead poisoning remains to be seen.

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