# Dose-response study of oral 2,3-dimercaptosuccinic acid in children with elevated blood lead concentrations

Joseph H. Graziano, PhD, Nancy J. Lolacono, MPH, and Patricia Meyer, MPH

From the Departments of Pharmacology and Pediatrics, Columbia University College of Physicians and Surgeons and Babies Hospital, New York

**2,3-Dimercaptosuccinic acid (DMSA) is an orally effective orphan drug that is more specific and has a wider therapeutic index than other currently available drugs used for lead intoxication. Its investigational use in the United States has been limited to the treatment of men with occupational plumbism. Twenty-one children with blood lead concentrations of 31 to 49 μg/dl, who also had a positive calcium disodium edetate ($CaNa_2EDTA$) mobilization test result, were hospitalized for 7 days. Fifteen children were randomly assigned to three groups that received either 350, 700, or 1050 mg/m²/day, respectively, of DMSA in three divided doses daily. A fourth group of six children received conventional treatment with 1000 mg/m²/day of intravenously administered $CaNa_2EDTA$ in two divided doses daily. The 1050 mg/m²/day dose of DMSA was significantly more effective than lower doses of DMSA or intravenously administered $CaNa_2EDTA$ in reducing blood lead levels and restoring erythrocyte δ-aminolevulinic acid dehydratase activity. Intravenously administered $CaNa_2EDTA$ significantly increased the urinary excretion of several essential minerals (zinc, copper, iron, and calcium), whereas DMSA did not. The DMSA was well tolerated and appears extremely promising as a drug that will simplify the management of childhood lead poisoning. (J PEDIATR 1988;113:751-7)**

Chelation therapy for children with lead poisoning has primarily relied on the parenteral use of calcium disodium edetate. Although effective in reducing the blood lead concentration and eliciting lead diuresis,[1,2] $CaNa_2EDTA$ is a relatively nonspecific chelator[3] that can be accompanied by renal toxic effects in patients who are not adequately hydrated.[4,5] Of greater concern, however, is that recent animal studies indicate that $CaNa_2EDTA$ can cause a redistribution of lead to the brain,[6] a finding that has led some to question the wisdom of using this drug in the "diagnostic" lead mobilization test.[6,7]

Other drugs for lead poisoning also have serious drawbacks. The intramuscular administration of 2,3-dimercaptosuccinic acid is associated with nausea and vomiting in the majority of children who receive it.[8] Because of its toxicity, BAL is administered only in conjunction with $CaNa_2EDTA$ to children with BPb concentrations of 70 μg/dl or more, who are at risk for encephalopathy.[5] To a

| | |
|---|---|
| ALA-D | δ-Aminolevulinic acid dehydratase |
| ANOVA | Analysis of variance |
| BAL | 2,3-Dimercapto-1-propanol (British antilewisite) |
| BPb | Blood lead concentration |
| $CaNa_2EDTA$ | Calcium disodium edetate |
| DMSA | 2,3-Dimercaptosuccinic acid |
| EP | Erythrocyte protoporphyrin |

Supported by grant No. MCJ-360509, awarded by the Division of Maternal and Child Health, Bureau of Health Care Delivery and Assistance, U.S. Public Health Service, and by grant No. RR-00645, from the General Clinical Research Centers Program of the Division of Research Resources.

Submitted for publication Feb. 3, 1988; accepted April 28, 1988.

Reprint requests: Joseph H. Graziano, PhD, Department of Pharmacology, Columbia University College of Physicians and Surgeons, 630 West 168th St., New York, NY 10032.

lesser extent, oral D-penicillamine has been used to treat children with moderately elevated BPb concentrations.[8,9] However, this agent is not nearly as effective as the former two drugs, is associated with allergic reactions, and is not approved by the U.S. Food and Drug Administration for use in children with lead poisoning. Finally, the use in children of 2,3-dimercapto-1-propanesulfonic acid,[10] a moderately effective oral analog of BAL, has been associated with serious toxic effects, and its use in this country has apparently been discontinued (J. Chisolm, Jr.: personal communication, July 15, 1987).

During the past 10 years, we have identified 2,3-dimercaptosuccinic acid as a potentially useful drug for the treatment of lead,[11,12] arsenic, and inorganic and organic mercury poisonings (reviewed by Graziano[13]). We report our experience with DMSA as a safe, specific, and highly effective oral agent for the treatment of elevated BPb levels in children.

## METHODS

Eligibility criteria for this protocol, which was approved by the Columbia Presbyterian Medical Center Institutional Review Board, consisted of a BPb level of 30 to 49 μg/dl and a positive $CaNa_2EDTA$ lead mobilization test result (i.e., >0.6 μg Pb/mg $CaNa_2EDTA$ administered). At the time that this study was initiated, standard therapy for such children[14] consisted of treatment with 1000 mg/m²/day of $CaNa_2EDTA$ administered intravenously in two divided doses daily for 5 days.

Parents were given the option to choose whether their child would receive conventional therapy with intravenously administered $CaNa_2EDTA$ or orally administered DMSA. Fifteen children whose parents granted informed consent for DMSA were randomly assigned to receive either 350, 700, or 1050 mg/m²/day of DMSA in three divided doses daily for 5 days. These doses of DMSA are equivalent to the doses of 10, 20, and 30 mg/kg/day, which had been studied in men with occupational lead poisoning.[12] The DMSA was provided in gelatin capsules containing 110 mg of active compound and was administered by emptying the contents of the capsules into either Hawaiian Punch or ice cream. (The dose of DMSA was rounded off to the nearest capsule, so the actual mean doses administered were 379, 714, and 1043 mg/m²/day.) In addition, six children whose parents consented to conventional therapy received 5 days of treatment with 1000 mg/m²/day of $CaNa_2EDTA$ given intravenously in two divided doses daily. Thus a total of 21 children were studied.

Exclusion criteria included the following: (1) known hypersensitivity to chelating agents, (2) a history or current findings of serious cardiovascular, renal, hepatic, endocrine, metabolic, or gastrointestinal disease, (3) any symptoms of serious lead poisoning, (4) an abnormal electrocardiogram, (5) the use of any investigational drug (including D-penicillamine) during the month before the initiation of the study, and (6) the use of any drug with well-defined organ toxicity (with the exception of $CaNa_2EDTA$) during the previous 6 months. Patients who had previously received $CaNa_2EDTA$ remained eligible to receive DMSA, and vice versa. Indeed, four children were studied twice, each receiving $CaNa_2EDTA$ or DMSA at different times, months apart; two received DMSA first and then $CaNa_2EDTA$, and two received $CaNa_2EDTA$ first and then DMSA.

Each child was admitted to the pediatric clinical research center for 7 days. During the first day, baseline blood and urine measurements were made. During the subsequent 5 days, either oral DMSA or intravenous $CaNa_2EDTA$ was administered: DMSA was administered at 8-hour intervals beginning at 2 P.M. on the second hospital day, and $CaNa_2EDTA$ was given at 12-hour intervals beginning at 11 A.M. of that day. The seventh day of hospitalization served as a posttreatment observation period. The protocol also called for each child to be seen as an outpatient approximately 1 and 2 weeks after discharge from the hospital. Twenty-four-hour urine specimens were collected daily (from 2 P.M. to 2 P.M.) throughout the 7-day hospital stay for the measurement of lead,[15] creatinine, and a variety of essential minerals.[16] In addition, blood samples were obtained daily for BPb,[17] erythrocyte δ-aminolevulinic acid dehydratase,[18] erythrocyte protoporphyrin,[19] and alanine and aspartate transaminase measurements. Complete blood cell counts were obtained once and serum chemistry panels were obtained twice before drug treatment (the second sample after an overnight fast). These analyses were repeated in the morning after 3 days of treatment, and in the morning after 5 days of treatment. Systolic and diastolic blood pressure, radial pulse (supine), and respiratory rate were recorded at 2:30 P.M., 10:30 P.M., and 6:30 A.M. on each day of the hospitalization.

Other drugs were administered only if absolutely necessary. Three patients who received DMSA (one patient per DMSA dosage group) received amoxicillin during the hospitalization for the treatment of otitis media. In addition, one patient in the $CaNa_2EDTA$ group received isoniazid during the hospitalization because of a positive purified protein derivative test result.

All 21 patients completed the hospitalization. One patient in the group receiving 350 mg/m²/day did not return for the scheduled follow-up visit 1 week after discharge from the hospital. Four patients did not return

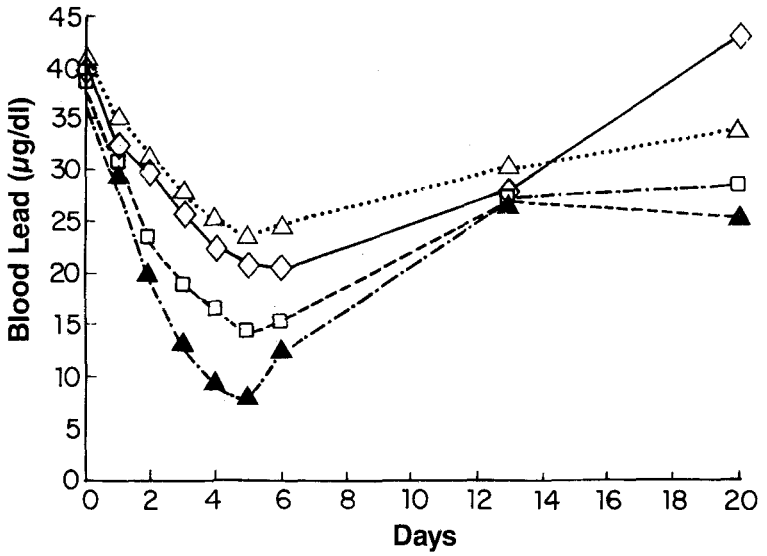


**Fig. 1.** Mean BPb concentrations of four treatment groups, illustrated as a function of time. Drugs were administered only on days 1 to 5. Groups are denoted as follows: Δ = 350 mg/m²/day DMSA; □ = 700 mg/m²/day DMSA; ▲ = 1050 mg/m²/day DMSA; ◇ = 1000 mg/m²/day $CaNa_2EDTA$. The ANOVA of the slopes of decline during days 0 to 5 found 1050 mg/m²/day of DMSA to be more effective than the other treatment regimens.

for the scheduled follow-up visit at 2 weeks after discharge; of these four patients, two were in the $CaNa_2EDTA$ group and two were in the group receiving 700 mg/m²/day DMSA.

**Statistical analysis.** With regard to BPb levels, the plan (a priori) was to conduct a regression analysis of BPb levels over time (for each patient) from day 0 (pretreatment) through day 5, with the use of both linear and nonlinear models. To force each regression curve through the same y-intercept, we also expressed the data as a percent of the pretreatment value; each patient was thus considered to be at 100% on day 0. One-way analysis of variance was then run on the 21 slopes of decline in BPb levels (i.e., four groups of patients). Differences between groups were evaluated by the Scheffé test for multiple comparisons, with an alpha statistic of 0.05.[20]

A similar analytic strategy was used for erythrocyte ALA-D. In this case the slopes were positive. Variables from complete blood cell counts, blood chemistry values, urinalyses, and vital signs were analyzed by three-way heirarchical ANOVA (group/subjects/days). The Scheffé test for multiple comparisons was subsequently used to examine differences between groups.

## RESULTS

**Demographic characteristics.** Of the 21 patients in the study, 14 were Hispanic, six were black, and only one was white. Patients who received $CaNa_2EDTA$ ranged in age from 2 to 5 years, and those who received DMSA were between 2 and 7 years of age; mean ages of the treatment groups ranged from 3.97 to 4.62 years. The mean pretreatment BPb concentration of the $CaNa_2EDTA$ group was 39.7 μg/dl, in comparison with 39.4, 37.5, and 36.0 μg/dl, respectively, for the groups that received 350, 750, and 1050 mg/m²/day DMSA. The mean EP level for the $CaNa_2EDTA$ group was 157 μg/dl, in comparison with 158, 86, and 143 μg/dl for the three DMSA groups, respectively. Thus all four treatment groups were comparable.

**Efficacy**

*Blood lead levels.* In each group, BPb levels declined during the 5-day treatment period and rebounded after the cessation of drug administration, presumably reflecting the mobilization of lead from the skeleton (Fig. 1). Regression analyses (over days 0 to 5) were conducted with BPb concentrations expressed in four different ways: (1) the raw BPb measurement, (2) log BPb, (3) percent of the pretreatment BPb level, and (4) log percent of initial BPb concentration. For each patient the correlation between BPb level and day of treatment was significant for each type of analysis. However, the data yielded the best fit when analyzed as log percent of the initial BPb level versus number of days of treatment.

The decline in BPb concentration obtained in response to the lowest dose of DMSA (350 mg/m²/day) did not differ from that observed in response to conventional

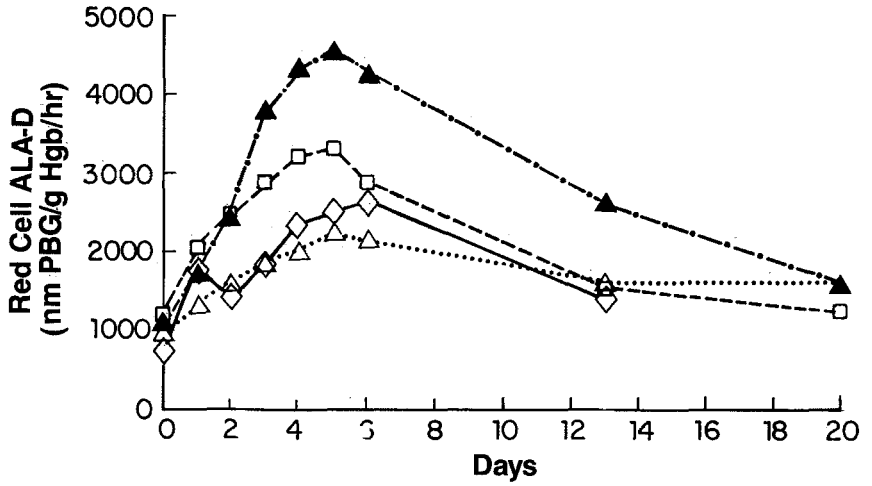


**Fig. 2.** Mean erythrocyte ALA-D activities of four treatment groups, illustrated as a function of time. Groups are denoted as follows: Δ = 350 mg/m²/day DMSA; □ = 700 mg/m²/day DMSA; ▲ = 1050 mg/m²/day DMSA; ◇ = 1000 mg/m²/day $CaNa_2EDTA$. The ANOVA of slopes of rise during days 0 to 5 found 1050 mg/m²/day of DMSA to be more effective than the other treatment regimens in restoring ALA-D activity. *PBG*, Porphobilinogen.

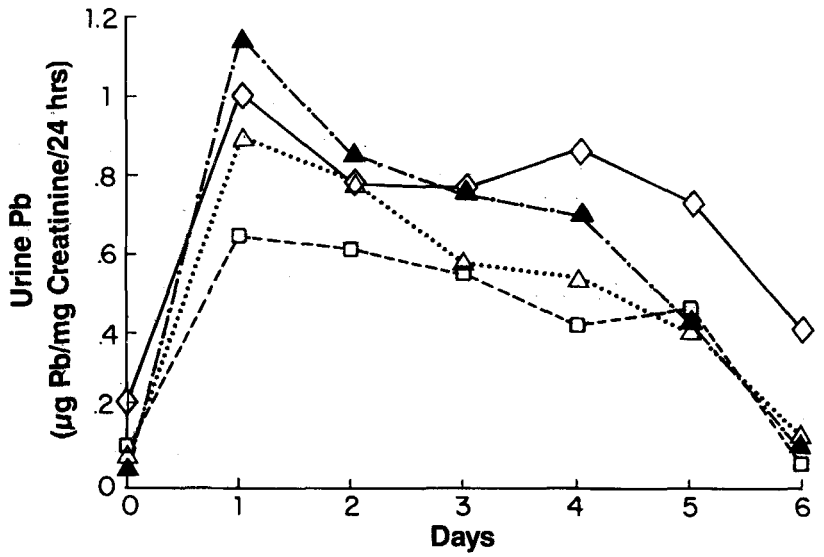


**Fig. 3.** Urinary lead data, expressed as micrograms of lead per milligram of urinary creatinine per 24 hours, of each treatment group during 7-day hospitalization. Drugs were administered only on days 1 to 5. Data are scattered because of the problem of incomplete urine collections. Groups are denoted as follows: Δ = 350 mg/m²/day DMSA; □ = 700 mg/m²/day DMSA; ▲ = 1050 mg/m²/day DMSA; ◇ = 1000 mg/m²/day $CaNa_2EDTA$. The ANOVA found creatinine-corrected urinary lead excretion to be greatest in group that received $CaNa_2EDTA$.

intravenous $CaNa_2EDTA$ treatment. However, the highest dose of DMSA (1050 mg/m²/day) was significantly more effective than either conventional intravenous $CaNa_2EDTA$ treatment or lower doses of DMSA.

*Erythrocyte ALA-D.* Measurement of ALA-D activity was done to provide an estimate of metabolic inhibition by lead. During the course of chelation therapy, erythrocyte ALA-D activity rose in all four treatment groups (Fig. 2). In each patient the slope of rise in erythrocyte ALA-D activity was calculated by regression analysis; each such individual analysis was highly significant. The highest dose of DMSA (1050 mg/m²/day) was significantly more effective in rejuvenating ALA-D activity than either lower doses of DMSA or conventional therapy with $CaNa_2EDTA$.

*Urinary lead excretion.* The collection of complete

**Table.** Mean urinary mineral excretion per milligram of creatinine

| | Day number | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
| Urinary Zn (μg) | | | | | | | |
| Group 1* | 0.9 | 0.9 | 1.1 | 0.9 | 1.2 | 1.4 | 0.9 |
| Group 2† | 0.8 | 1.2 | 1.1 | 1.2 | 1.2 | 1.3 | 1.1 |
| Group 3‡ | 1.5 | 1.2 | 1.6 | 1.3 | 1.6 | 1.8 | 1.2 |
| Group 4§ | 3.8 | 12.7 | 13.3 | 13.5 | 11.5 | 12.9 | 3.6 |
| Urinary Cu (μg) | | | | | | | |
| Group 1 | 0.37 | 0.26 | 0.29 | 0.22 | 0.37 | 0.36 | 0.44 |
| Group 2 | 0.38 | 0.39 | 0.37 | 0.40 | 0.29 | 0.47 | 0.73 |
| Group 3 | 0.39 | 0.47 | 0.55 | 0.41 | 0.53 | 0.73 | 0.47 |
| Group 4 | 0.65 | 1.13 | 1.16 | 0.74 | 0.88 | 0.98 | 0.72 |
| Urinary Fe (μg) | | | | | | | |
| Group 1 | 1.0 | 1.1 | 0.8 | 1.0 | 1.4 | 1.5 | 1.1 |
| Group 2 | 1.0 | 1.5 | 1.0 | 1.0 | 0.8 | 1.5 | 1.9 |
| Group 3 | 1.1 | 0.8 | 1.3 | 0.9 | 1.2 | 2.0 | 1.6 |
| Group 4 | 1.8 | 2.2 | 2.5 | 1.9 | 2.1 | 2.7 | 1.5 |
| Urinary Ca (μg) | | | | | | | |
| Group 1 | 43 | 26 | 28 | 72 | 64 | 60 | 60 |
| Group 2 | 56 | 55 | 89 | 94 | 110 | 78 | 79 |
| Group 3 | 55 | 68 | 121 | 107 | 88 | 94 | 102 |
| Group 4 | 110 | 137 | 192 | 241 | 171 | 162 | 119 |
| Urinary Mg (μg) | | | | | | | |
| Group 1 | 128 | 100 | 89 | 110 | 130 | 122 | 114 |
| Group 2 | 73 | 108 | 126 | 109 | 96 | 135 | 136 |
| Group 3 | 176 | 150 | 181 | 111 | 142 | 160 | 102 |
| Group 4 | 120 | 129 | 102 | 87 | 81 | 55 | 69 |

There was a significant group effect ($p < 0.001$) for urinary Zn, Cu, Fe, and Ca. In each case, the $CaNa_2EDTA$ group was found to differ significantly from all three DMSA dose groups. The increase in urinary Ca excretion in the $CaNa_2EDTA$ group is probably due to the renal elimination of $CaNa_2EDTA$.
*Group 1: 350 mg/m²/day DMSA.
†Group 2: 700 mg/m²/day DMSA.
‡Group 3: 1050 mg/m²/day DMSA.
§Group 4: 1000 mg/m²/day $CaNa_2EDTA$.

24-hour urine specimens in these very young children, many not toilet trained, was not always a complete success. Accordingly, all urine data must be reviewed cautiously. For all urine variables, we attempted to adjust for urine losses by also expressing the data per milligram of urinary creatinine. This correction assumes that urinary lead excretion is relatively constant throughout the day; this assumption may not be accurate.

There were no significant differences among treatment groups with regard to *pretreatment* urinary lead excretion (expressed as micrograms of Pb per milligram of creatinine) on day 0. With regard to this value during the course of treatment, ANOVA revealed a significant dose effect ($p < 0.0001$) and a significant dose-by-day interaction ($p < 0.0001$) (Fig. 3). The Scheffé test for multiple comparisons found the urinary Pb excretion to be higher in the $CaNa_2EDTA$ group than in each of the three DMSA groups. The dose-by-day interaction reflected decreasing lead excretion over time, undoubtedly a consequence of the gradual decline of lead concentrations in the blood and soft tissue compartments.

**Specificity.** There were no significant differences among groups in the urinary excretion of Mg, Zn, Cu, Fe, and Ca on day 0, before drug administration. (Because the first dose of $CaNa_2EDTA$ was administered at 11 A.M., 3 hours before the completion of the first 24-hour urine collection, the values for day 0 excretion of Zn, Cu, Fe, and Ca were highly variable and appeared slightly elevated in comparison with those for the DMSA treatment groups.) $CaNa_2EDTA$ induced significant rises in urinary Zn, Cu, Fe, and Ca excretion (Table); the latter may be because this drug contains calcium. The magnitude of the effects of $CaNa_2EDTA$ on urinary mineral excretion was small for Cu and Fe but large and clinically significant for Zn. Treatment with DMSA did not cause a significant elevation in the excretion of any of these essential trace minerals. These findings indicate that DMSA is far more specific than $CaNa_2EDTA$ for heavy metals.

**Safety.** No clinically significant abnormal complete blood cell counts, vital signs, or clinical chemistry values were observed. Daily measurements of alanine and aspartate transaminase were normal. (In a previous study of

DMSA in men with occupational plumbism,[12] three patients had experienced a very mild transient rise in alanine transaminase.

For each of the following measurements, three-way ANOVA was conducted: serum Na, K, Cl, $CO_2$, blood urea nitrogen, glucose, creatinine, Ca, P, uric acid, cholesterol, protein, albumin, total bilirubin, direct bilirubin, alkaline phosphatase, lactate dehydrogenase, creatine phosphokinase, alanine and aspartate transaminase, hemoglobin, hematocrit, erythrocyte and leukocyte counts, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, systolic and diastolic blood pressure, radial pulse, respiratory rate, and body temperature. Several findings were statistically significant but no trends were noted, and none of the findings was of clinical significance, because all values were within normal ranges.

Administration of DMSA was well tolerated by all 15 children. Two patients who had also received amoxicillin, one in the low-dose DMSA group and one in the high-dose group, had a single episode of vomiting. In one child, it followed the very first dose of DMSA; in the other child it occurred on day 4 of treatment. Each child eventually completed the course of treatment without further incident. No other adverse effects were observed.

## DISCUSSION

2,3-Dimercaptosuccinic acid was first synthesized by Friedheim and DaSilva,[21] who incorporated the molecule into the structure of melarsonyl potassium (also known as Mel W), an arsenical drug for the treatment of schistosomiasis. It was first proposed as an antidote for heavy metal poisoning by the Chinese[22, 23] and has been used fairly widely in the People's Republic of China, the Soviet Union, and Japan (reviewed by Aposhian[24]). Our recent work has fueled interest in this neglected compound, now classified as an orphan drug by the U.S. Food and Drug Administration. We have expanded the clinical experience with DMSA while paying particular attention to dose requirements, its safety in both adults[12] and children, and its efficacy in comparison with other chelating agents.

Perhaps the most important findings of this study are that, at doses of 700 or 1050 mg/m$^2$/day, DMSA brings about a more substantial decrease in BPb concentrations than does $CaNa_2EDTA$, whereas $CaNa_2EDTA$ evokes a greater urinary lead output. There are two possible explanations for this apparent contradiction. First, DMSA could conceivably shift lead from the blood compartment to other tissues rather than into the urine; however, animal data indicate that this is not the case.[11, 25] The second possibility, supported by a considerable body of evidence, is that $CaNa_2EDTA$ brings about a substantial mobilization of lead from bone, resulting in the movement of lead into the blood, soft tissues, and urine. The rapid mobilization of lead from bone by $CaNa_2EDTA$ appears to be potentially dangerous. For example, Cory-Slechta et al.[6] demonstrated that a single dose of $CaNa_2EDTA$ can increase brain and liver lead concentrations. Chisolm's clinical experience[1, 2, 7] during the 1950s in children with acute lead encephalopathy and BPb concentrations >150 μg/dl demonstrated a temporary worsening of central nervous system manifestations after the initiation of $CaNa_2EDTA$ treatment.

Thus, although the mobilization of lead from bone by $CaNa_2EDTA$ results in more urinary lead excretion than is observed with DMSA treatment, the use of $CaNa_2EDTA$ does not result in a greater reduction in lead poisoning and is not clinically more beneficial. An analogy to this finding relates to the use, during the early 1970s, of ascorbic acid to increase the urinary elimination of iron in response to deferoxamine therapy in patients with thalassemia major.[26] Although ascorbic acid undoubtedly increased iron mobilization and urinary iron output, it was not beneficial and, in fact, resulted in the death of several patients from cardiac disease because of the redistribution of iron to the heart.[27, 28]

Including the 15 children who are subjects of this report, our institution has now used oral DMSA to treat 50 individuals, ages 1 to 58 years, with BPb levels ranging from 31 to 96 μg/dl, without any serious adverse effects. The drug appears safe, effective, specific, and simple to administer, and it thus represents a significant improvement over existing drugs for the treatment of lead poisoning. We caution, however, that little is known about the safety of longer courses of therapy; in 43 of our 50 patients, the duration of DMSA administration was limited to a single 5-day course of therapy. Further studies of DMSA, involving longer courses of therapy on an outpatient basis, are in progress.

We thank Drs. Sergio Piomelli, Michele Denize, Steven Arkin, Karen Bye, and Millicent Sutton, who provided clinical care for these patients. We thank the nursing staff of the Pediatric Clinical Research Center for their expert assistance, and Don McMahon, Edith Flaster, Diane Furnham, Vera Gisoldi, Beatrix Dinitz, Ivy Fonseca, and Grace Peguero for their expert technical assistance. Thanks to Dr. Mary Murphy for her critical review of this manuscript. Finally, we thank the Baby Products Company of Johnson & Johnson for the supply of DMSA.

## REFERENCES

1. Chisolm JJ Jr. The use of chelating agents in the treatment of acute and chronic lead intoxication in childhood. J PEDIATR 1968;73:1-38.
2. Chisolm JJ Jr. Treatment of lead poisoning. Mod Treat 1971;8:593-611.

3. Perry HM Jr, Perry EE. Normal concentrations of some trace metals in human urine: changes produced by ethylenediaminetetraacetate. J Clin Invest 1959;38:1452-63.
4. Foreman H, Finnegan C, Lushbaugh CC. Nephrotoxic hazard from uncontrolled edathamil calcium disodium therapy. JAMA 1956;160:1042-6.
5. Piomelli S, Rosen JF, Chisolm JJ Jr, Graef JW. Management of childhood lead poisoning. J PEDIATR 1984;105:523-32.
6. Cory-Slechta DA, Weiss B, Cox C. Mobilization and redistribution of lead over the course of CaEDTA chelation therapy. J Pharmacol Exp Ther 1987;243:804-13.
7. Chisolm JJ Jr. Mobilization of lead by calcium disodium edetate: a reappraisal. Am J Dis Child 1987;141:1256-7.
8. Klaassen CD. Heavy metals and heavy-metal antagonists. In: Gilman AG, Goodman LS, Gilman A, eds. The pharmacological basis of therapeutics, New York: Macmillan, 1980:1615-37.
9. Shannon M, Graef J, Lovejoy FH Jr. Efficacy and toxicity of D-penicillamine in low-level lead poisoning. J PEDIATR 1988;112:799-804.
10. Chisolm JJ Jr, Thomas DJ. Use of 2,3-dimercaptopropane-1-sulfonate in treatment of lead poisoning in children. J Pharmacol Exp Ther 1985;235:665-9.
11. Graziano JH, Leong JK, Friedheim E. 2,3-Dimercaptosuccinic acid: a new agent for the treatment of lead poisoning. J Pharmacol Exp Ther 1978;206:696-700.
12. Graziano JH, Siris ES, Lolacono N, Silverberg SJ, Turgeon L. 2,3-Dimercaptosuccinic acid as an antidote for lead intoxication. Clin Pharmacol Ther 1985;37:431-8.
13. Graziano JH. Role of 2,3-dimercaptosuccinic acid in the treatment of heavy metal poisoning. Med Toxicol 1986;1:155-62.
14. Centers for Disease Control. Preventing lead poisoning in young children. DHEW publication No. 00-2620. Washington, D.C.: U.S. Government Printing Office, 1978.
15. Searle B, Chan W, Davidow B. Determination of lead in blood and urine by anodic stripping voltammetry. Clin Chem 1973;19:76-80.
16. Graziano JH, Grady RW, Cerami A. The identification of 2,3-dihydroxybenzoic acid as a potentially useful iron-chelating drug. J Pharmacol Exp Ther 1974;190:570-5.
17. Fernandez F, Hilligoss D. An improved graphite furnace method for the determination of lead in blood using matrix modification and the L'vov platform. Atomic Spectroscopy 1982; 3:130-1.
18. Weissberg JB, Lipshutz F, Oski F. Delta-aminolevulinic acid dehydratase activity in circulating blood cells: a sensitive laboratory test for the detection of childhood lead poisoning. N Engl J Med 1971;284:565-9.
19. Piomelli S. A micromethod for free erythrocyte porphyrins: the FEP test. J Lab Clin Med 1973;81:932-40.
20. Scheffé H. The analysis of variance. New York: John Wiley & Sons, 1967.
21. Friedheim EAH, DaSilva JR. Treatment of schistosomiasis mansoni with antimony a,á-dimercapto-potassium succinate (TWSb). Am J Trop Med Hyg 1954;3:714-27.
22. Ting KS, Liang YI, Shi J, Chen W, Gu T. Chelate stability of sodium dimercaptosuccinate on the intoxications from many metals. Chin Med J [Engl] 1965;51:304-7.
23. Wang SC, Ting KS, Wu CC. Chelating therapy with NaDMS in occupational lead and mercury intoxication. Chin Med J [Engl] 1965;84:437-9.
24. Aposhian HV. DMSA and DMPS: water-soluble antidotes for heavy metal intoxication. Ann Rev Pharmacol Toxicol 1983;23:193-215.
25. Bankowska J, Hine C. Retention of lead in the rat. Arch Environ Contam Toxicol 1985;14:621-9.
26. O'Brien R. Ascorbic acid enhancement of desferrioxamine-induced urinary iron excretion in thalassemia major. Ann NY Acad Sci 1974;232:221-5.
27. Niehhuis A. Safety of intensive chelation therapy. N Engl J Med 1977;296:114.
28. Graziano JH, Cerami A. Chelation therapy for the treatment of thalassemia. Semin Hematol 1977;14:127-34.