Short-Term Efficacy of Oral Dimercaptosuccinic Acid in Children With Low to Moderate Lead Intoxication

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ABSTRACT. *Objective.* **To determine the short-term efficacy of meso-2,3-dimercaptosuccinic acid (DMSA) in mild to moderately lead poisoned children.**

Methods. **Medical records of all pediatric patients receiving 19 days of DMSA between June 1991 and May 1993 were reviewed retrospectively. Patients were included if their pretreatment blood lead concentration (BPb) was 1.21 to 2.36 μmol/L (25 to 49 μg/dL) and excluded if they: received DMSA through participation in a pharmaceutical company-sponsored drug study; underwent chelation therapy in the previous 28 days; or received another chelating agent concomitantly with DMSA; or if noncompliance was documented. Homes were inspected and abated of major hazards before chelation therapy. BPb and blood zinc protoporphyrin concentration (ZnP) were obtained at baseline. DMSA was administered in a dose approximating 10 mg/kg per dose every 8 hours for 5 days, followed by 10 mg/kg per dose every 12 hours for 14 days. Baseline laboratory studies were repeated weekly while the patients were receiving therapy and for 2 weeks after therapy, then monthly unless chelated again.**

Results. **Of the 46 children who were treated with DMSA, 18 were excluded from the analysis. In the remaining 28 children, the mean ± SD pretreatment BPb and ZnP were 1.79 ± 0.33 μmol/L (37 ± 6.9 μg/dL) and 1.26 ± 0.64 μmol/L (71 ± 36.1 μg/dL), respectively. The percent reduction (mean ± SD) in BPb compared with baseline was −43% ± 20.8%, −26% ± 16.9%, and −31% ± 20.2% on mean days 18, 30, and 80, respectively, whereas the changes in ZnP were −12% ± 21.7%, −20% ± 18.1%, and −32% ± 21.9%, respectively. Eighty percent of patients had 20% or more reduction in their pretreatment BPb and/or ZnP after completion of DMSA therapy (95% confidence interval, 61, 92%). No significant adverse effects were observed except for neutropenia (absolute neutrophil count of 0.752 × 10^9/L) in one patient.**

Conclusion. **Our findings support the short-term efficacy of DMSA in children with BPb of 2.36 μmol/L (49 μg/dL) or less.** *Pediatrics* **1995;96:683–687;** ***lead poisoning, chelation therapy, dimercaptosuccinic acid, zinc protoporphyrin.***

ABBREVIATIONS. BPb, whole-blood lead concentration; DMSA, meso-2,3-dimercaptosuccinic acid; EDTA, calcium disodium ethylenediaminetetraacetic acid; ZnP, whole-blood zinc protoporphyrin concentration; ALT, alanine aminotransferase; CI, confidence interval.

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Despite growing concerns regarding the detrimental effects of low to moderate levels of lead intoxication in children, pharmacologic treatment of children with a whole-blood lead concentration (BPb) of less than 2.17 μmol/L (45 μg/dL) is controversial. The cornerstone of therapy remains prevention, which includes identification of lead sources, abatement, and counseling of families as to ways of minimizing further exposure. Lead that already has accumulated, however, is only slowly eliminated from the body.[1,2] For example, Shannon et al[2] observed no change in BPb during a mean period of 60 days in 84 children who subsequently underwent chelation with penicillamine. Meso-2,3-dimercaptosuccinic acid (DMSA) is an oral analog of dimercaptopropanol that is approved by the Food and Drug Administration for the treatment of children with BPb of 2.17 μmol/L or greater. It seems to have a wide therapeutic index, may promote less urinary excretion of essential minerals than calcium disodium ethylenediaminetetraacetic acid (EDTA),[3,4] and in animals does not increase intestinal absorption of lead.[5] To date there is only one published study reporting the use of a 19-day treatment course of DMSA in children with BPb of 2.36 μmol/L (49 μg/dL) or less.[6] In this study, a 19-μg/dL decline in BPb was noted during the treatment period. Neither the response of whole-blood zinc protoporphyrin concentration (ZnP) to oral chelation nor the percentage of patients responding to treatment were reported. The purpose of our study is to confirm and expand on the findings in the previous study plus to report the response of ZnP to a 19-day treatment course in children with BPb of 2.36 μmol/L or less.

METHODS

Medical records of all pediatric patients followed in the Lead Clinic at MetroHealth Medical Center between June 1991 and May 1993 and treated with DMSA were reviewed retrospectively. Patients were included in the study if their pretreatment BPb was 1.21 to 2.36 μmol/L (25 to 49 μg/dL). Several patients received more than one treatment course with DMSA, but only data from the initial course were included. Patients were excluded if they: received DMSA through participation in a pharmaceutical company-sponsored drug study; underwent chelation therapy in the previous 28 days; or received another chelating agent concomitantly with DMSA; or if the medical record clearly documented noncompliance with the drug regimen. Home inspection, which included visual inspection of the interior and exterior of the home and x-ray fluorescence of painted surfaces, was performed by the patient's local health department, and abatement of major sources of lead (ie, peeling or cracking paint) was accomplished before chelation therapy. Families were also counseled on methods to minimize further exposure to lead primarily from household dust and soil. As per the protocol in our lead clinic, the following

laboratory and radiographic studies were obtained before initiating therapy: whole blood BPb and ZnP, complete blood count and white blood cell differential, blood urea nitrogen, serum creatinine, serum liver function studies (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase), urinalysis, a flat-plate radiograph of the abdomen (kidneys, ureters, bladder), and serum iron studies (iron, total iron-binding capacity, and ferritin). Children then received a dose of DMSA approximating 10 mg/kg per dose every 8 hours for 5 days, followed by 10 mg/kg per dose every 12 hours for the next 14 days. No patient received iron concomitantly with DMSA. Data from all follow-up visits were recorded. Patients were followed approximately weekly while receiving therapy and for 2 weeks after therapy, then monthly unless chelated again. All baseline laboratory studies except iron studies and the urinalysis were repeated at each follow-up visit. Patients were included for analysis if a pretreatment BPb and at least one postchelation BPb within 5 weeks of starting treatment were recorded in the medical record. Data were categorized a priori in relation to the first day of drug treatment (day 1). The categories, followed in parentheses by the range in which the sample was obtained, are: pretreatment (within 30 days of commencing therapy); day 7 (days 4 to 10); day 14 (days 11 to 17); day 21 (days 18 to 24); day 28 (days 25 to 31); and day 35 (days 32 to 38). Data obtained approximately 1 and 2 months after the day 35 visit were also recorded and analyzed.

BPb was measured by atomic absorption spectroscopy (atomic absorption spectrophotometer; Varian Co, Varian Analytical Instruments, Sugar Land, TX) with a coefficient of variation of less than 10%. ZnP was measured by hematofluorometer (ESA Inc, Bedford, MA).

The percent change in BPb and ZnP at subsequent time points was determined by $(BPb_{time\ 2} - BPb_{time\ 1}) \times 100/BPb_{time\ 1}$ and $(ZnP_{time\ 2} - ZnP_{time\ 1}) \times 100/ZnP_{time\ 1}$. DMSA responders were defined a priori as children whose day 35 BPb fell by 20% or more from pretreatment levels.

Statistical Analysis

Interval level data are reported as means ± SDs. Paired parametric data were analyzed with the paired *t* test. Paired nonparametric interval level data and paired ordinal level data were compared with the Wilcoxon signed rank test. Patient characteristics between the responders and nonresponders were compared by the Mann Whitney *U* test. Pearson correlation and linear regression analysis were used to evaluate the following relationships: change in BPb with pretreatment variables of age, dose, serum ferritin concentration, hemoglobin concentration, BPb and ZnP; change in ZnP with pretreatment variables of BPb, ZnP, serum ferritin and hemoglobin concentrations; change in BPb during therapy with change in ZnP; pretreatment ZnP with pretreatment serum ferritin and hemoglobin concentrations; and percent rebound in BPb with all pretreatment variables. On examining the residuals from the above regression analyses, the assumptions of linearity and equality of variance were met. In addition, no potential outliers were identified by Cook's and Mahalanobis' distances. Mahalanobis' distance identifies a potential outlier by computing the square of the standardized values of the independent variable, whereas Cook's distance determines whether the potential outlier is an influential case by examining the residuals when that case is both included and excluded from the analysis. For correlations and linear regression analysis, the sample size was sufficient to detect an $r \geq .5$ with a two-tailed α of .05 and β of .20. Data were analyzed using the SPSSPC version 4.0 (SPSS Inc, Chicago, IL) software package. For proportions, the 95% confidence intervals (CIs) are reported.[7] All statistical tests are two-tailed. Statistical significance was set a priori at $P < .05$.

RESULTS

Forty-six children with BPb of 2.36 µmol/L or less were treated with DMSA. Eighteen were excluded from analysis: 14 participated in a pharmaceutical company-sponsored drug study; 3 received EDTA with the initial 5 days of DMSA therapy; and 1 patient was noncompliant. Characteristics of the remaining 28 patients before treatment are summarized in Table 1. Fifteen children were boys, and 15 were black, 10 white, and 3 hispanic. Four patients received chelation therapy with EDTA and dimercaptopropanol 1 to 4.5 months before treatment with DMSA.

TABLE 1. Patient Characteristics*

Parameter	Mean	Range
Age (mo)	44.0 ± 28.6	12–147
Blood lead (µg/dL)	37 ± 6.9	26–49
Blood ZnP (µg/dL)	71 ± 36.1	29–182
Dose (mg/kg)	10.0 ± 2.5	6.8–14.7
Hgb (g/dL)	11.8 ± 1.0	10.4–14.5
Ferritin (ng/mL)	29.8 ± 16.1	5–72.6

* Laboratory studies represent pretreatment values. For conversion to SI units: BPb, 1 µg/dL = 0.04826 µmol/L; ZnP, 1 µg/dL = 0.0177 µmol/L; Hgb, 1 g/dL = 0.6206 mmol/L; and ferritin, 1 ng/mL = 1 µg/L.

Pretreatment laboratory values were obtained on the average of 8 days before the start of therapy (range, 0 to 22 days). BPb fell abruptly during the first week of therapy then remained constant through the remainder of the 19-day treatment course (Fig 1). The BPb then rose during the next 2 weeks, followed by a slight decrease during the following 2 months. The BPb on mean days 66 and 93 were not significantly lower than the BPb on day 34 ($P = .14$ and .27, respectively). In contrast, the ZnP gradually declined during the first 5 weeks before stabilizing (Fig 1). The difference in ZnP from pretreatment values achieved statistical significance by day 14 but was greatest at mean day 34. The ZnP on mean days 66 and 93 were not significantly lower than on day 34 ($P = .50$ and .47, respectively).

Because there were no statistically significant differences between the BPb and ZnP on day 14 vs 21, 28 vs 34, and 66 vs 93, and because all patients did not have evaluable data at each scheduled visit, the data from these follow-up days were combined and hence reported as BPb and ZnP on mean days 18, 30, and 80. In addition, DMSA responders were rede-

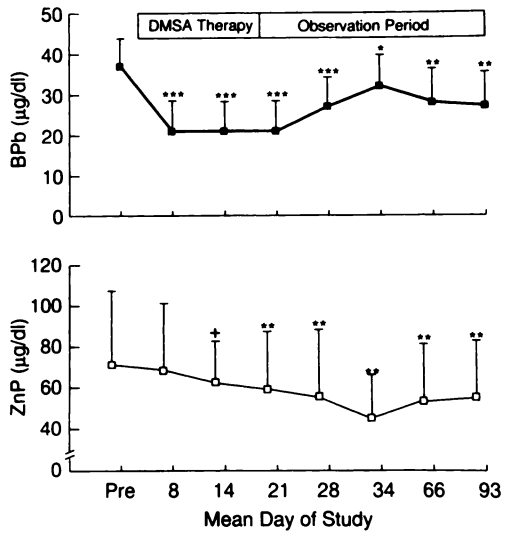

Fig 1. Relationship between BPb and ZnP concentrations and mean day of study. Vertical bars represent SDs. Pre, pretreatment values. ***$P < .001$; **$P < .005$; *$P < .01$; +$P < .05$ compared with pretreatment.

fined as children whose day 30 BPb fell by 20% or more from pretreatment. The percent reduction in BPb compared with baseline was −43% ± 20.8%, −26% ± 16.9%, and −31% ± 20.2% on mean days 18, 30, and 80, respectively, whereas the changes in ZnP were −12% ± 21.7%, −20% ± 18.1%, and −32% ± 21.9%, respectively.

The changes in BPb and ZnP were greater between pretreatment and day 30 than between days 30 and 80 (Fig 2). To determine whether the rate of change of BPb or ZnP differed during these time periods, the slopes of the mean BPb versus time curve and the mean ZnP versus time curve from pretreatment to day 30 ([BPb or $ZnP_{day\ 30}$] − [BPb or $ZnP_{pretreatment}$]/ days between two blood samples) were compared with the respective slopes of the curves from day 30 to 80 ([BPb or $ZnP_{day\ 80}$] − [BPb or $ZnP_{day\ 30}$]/days between two blood samples). The slope from pretreatment to day 30 was sevenfold greater for BPb compared with days 30 to 80 ($P = .008$) and threefold greater for ZnP ($P = .078$). The changes in BPb and ZnP were not related to any pretreatment variable.

Twenty-one of the 28 patients had evaluable BPb and ZnP after rebound on mean day 30. The ZnP was lower than the pretreatment value in all but 1 patient whose ZnP was unchanged. The BPb was lower than the pretreatment concentration on day 30 in 19 patients. The other 2 patients did have falls in their BPb during therapy (from 30 to 16 μg/dL and 47 to 17 μg/dL on day 18), but it rebounded markedly after the completion of treatment (16 to 30 μg/dL and 17 to 50 μg/dL, respectively). However, in these 2 patients the ZnP fell from 38 to 25 μg/dL and 107 to 56 μg/dL, respectively, by day 30. Thirteen of the 21 patients had 20% or more falls in BPb (95% CI, 39, 81%) (Fig 3). Of the 8 patients whose BPb changed by less than 20% on day 30, 4 had 20% or more reductions from baseline in ZnP on day 30. Of the 7 patients without a BPb on day 30, 6 had a BPb obtained on day 80. Five of these 6 patients had more than 20% reductions in BPb from their baseline value. Therefore, approximately 80% of patients had a 20% or more change in either BPb or ZnP during follow-up (95% CI, 61, 92%).

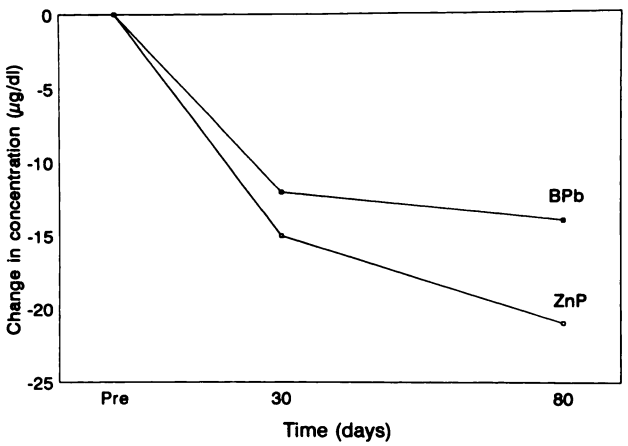

Fig 2. Change in BPb and ZnP concentrations during the treatment and rebound period (before day 30) and the postrebound observation period (days 30 to 80) in children with pretreatment, day 30, and day 80 BPb and ZnP. Pre, pretreatment values.

In the 21 patients with evaluable BPb for mean day 30, the DMSA responders were compared with the nonresponders with regard to their baseline BPb and ZnP, percent change of BPb and ZnP during therapy, and percent change after therapy (Table 2). Only the mean percent changes in BPb on day 30 were significantly different between the 2 groups.

Posttreatment hemoglobin, absolute neutrophil count, and ALT did not differ from pretreatment values. Two patients had 1-g/dL (0.62 mmol/L) decrements in their hemoglobin concentrations, and one patient's absolute neutrophil count fell to 0.752×10^9/L during therapy with no other apparent cause. These three patients remained asymptomatic. No patient had a rise in liver enzymes above the normal range (normal ranges: ALT, 7 to 40 IU/L; AST, 7 to 40 IU/L; and alkaline phosphatase, 100 to 400 IU/L).

DISCUSSION

In our study of 28 children with low to moderate lead intoxication, DMSA administration resulted in a 43% reduction in BPb during treatment. After therapy the BPb remained from 26% to 31% lower than the pretreatment values. These results are similar to the previous two DMSA chelation studies on children with low to moderate lead toxicity[6] and moderate to high levels of intoxication.[4] In the study by Graziano et al,[4] 1050 mg/m² per day was administered for 5 days to hospitalized children with BPb of 2.41 to 3.33 μmol/L (50 to 69 μg/dL). Six children then received 700 mg/m² per day for 14 days. During treatment the BPb fell by approximately 50%, and by 2 weeks after completing treatment, it was 23% lower than the pretreatment concentration. Liebelt et al,[6] using a similar dose and treatment course as in our study, reported a 60% decline in BPb during therapy in 23 children with baseline BPb of 0.97 to 2.17 μmol/L (20 to 45 μg/dL). After therapy, the changes in BPb were 30% and 26% on days 41 and 67, respectively, compared with pretreatment. Neither of these studies, however, reported changes in erythrocyte protoporphyrin concentrations with therapy or the number of children who demonstrated an efficacious response to therapy.

The efficacy of lead chelation therapy has never been defined in the literature. One of the major limitations in defining efficacy is the absence of a reliable, simple, and inexpensive method to quantify either total body lead stores or clinical toxicity. A change in BPb is the simplest way of defining efficacy, but it does not necessarily reflect changes in tissue lead stores or toxicity. The erythrocyte protoporphyrin concentration reflects the toxic effect of lead on heme synthesis and/or the effect of iron deficiency. The erythrocyte protoporphyrin concentration therefore may be helpful in defining toxicity. Nineteen of our 21 patients with measured BPb on day 30 had reductions in their BPb. The BPb in the other 2 patients did fall during therapy but then rebounded markedly. This rebound could be attributed to redistribution of lead from soft tissue and bone or from reexposure to lead. In both cases the ZnP fell significantly. The change in ZnP most likely represented a reduction in lead toxicity and not a

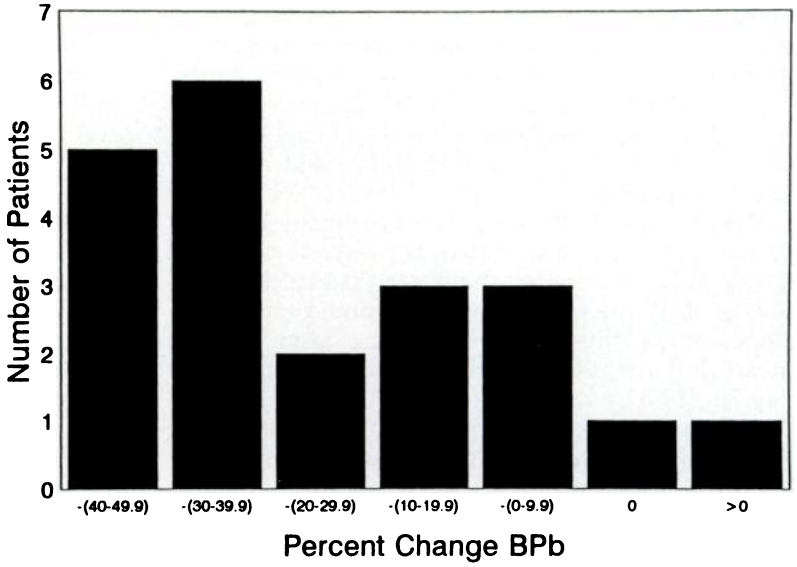

Fig 3. Number of children in different percentiles of change in BPb on mean day 30 compared with the pretreatment value.

TABLE 2. Characteristics of DMSA Responders* and Nonresponders†

	Responders (n = 13)	Nonresponders (n = 8)	*P* Value‡
Age (mo)	51.6 ± 36.0	40.3 ± 20.0	NS
Dose (mg/kg)	9.8 ± 2.4	10.1 ± 2.4	NS
Blood lead (μg/dL)§	39 ± 6.4	39 ± 7.1	NS
Zinc protoporphyrin (μg/dL)§	58 ± 28.5	73 ± 24.3	.105
Ferritin (ng/mL)§	31.8 ± 14.3	27.2 ± 24.2	NS
Hemoglobin (g/dL)§	11.6 ± 0.8	12.0 ± 1.3	NS
Percent change BPb during therapy‖	52 ± 19.9	36 ± 16.6	.09
Percent change BPb after rebound¶	37 ± 7.6	7.0 ± 8.8	<.001
Percent change ZnP post rebound¶	18 ± 20.4	23 ± 14.9	NS

Note: 21 of original 28 patients had evaluable BPb on day 30.
* ≥20% reduction in BPb on mean day 30 compared with pretreatment.
† <20% reduction in BPb on mean day 30 compared with pretreatment.
‡ Mann-Whitney *U* test.
§ Pretreatment laboratory values. For conversion to the SI units: BPb, 1 μg/dL = 0.04826 μmol/L; ZnP, 1 μg/dL = 0.0177 μmol/L; ferritin, 1 ng/mL = 1 μg/L; and homoglobin, 1 g/dL = 0.6206 mmol/L.
‖ Percent reduction mean day 18 compared with baseline.
¶ Percent reduction mean day 30 compared with baseline.

repletion of iron stores, because one patient had sufficient stores before therapy, and the other started to receive iron therapy after day 35 for a borderline deficiency state (serum ferritin, 13 ng/mL; normal range, 7 to 140 ng/mL). In our study population, the ZnP on mean day 30 was lower than the pretreatment value in all but 1 patient, whose ZnP was unchanged. No patient received iron until the course of therapy with DMSA was completed. Also, none of the 4 patients with a 0% to 20% decline in BPb and a 20% or greater fall in ZnP on mean day 30 received iron before day 30. This again strongly suggests that the fall in ZnP in our patients was attributable to a diminution in biochemical toxicity secondary to lead rather than a change in iron status. If efficacy of chelation therapy were redefined as either a 20% or greater reduction in BPb after rebound or a 20% or greater fall in ZnP with a 0% to 20% decline in BPb, then 80% of our patients had a beneficial response to chelation therapy. No variable was identified that would distinguish responders from nonresponders. However, the power of our study was insufficient for detecting a statistically significant difference in the pretreatment ZnP and the change in BPb during therapy between these two groups.

Because we did not have a control group, it is possible that the changes in BPb and ZnP were attributable to factors other than chelation therapy, particularly lead abatement. It is our opinion, however, that DMSA therapy contributed significantly to the changes, as evidenced by the rapid fall in BPb during the first week of treatment, the marked difference in the rate of change in BPb between days 0 and 30 and 30 and 80, and the insignificant change in BPb and ZnP during the postrebound observation period. Furthermore, there was a trend toward a steeper rate of change in ZnP during the first 30 days despite the institution of iron supplementation only after DMSA therapy was completed. This therapy would have favored a greater rate of change in ZnP after day 30. This opinion is supported by previous studies.[2,8] Shannon et al[2] did not find a significant change in either BPb or ZnP during a mean observation period of 60 days in children whose homes were either abated or for whom alternative housing was found. The mean BPb and ZnP were significantly

lower in those children who were subsequently chelated with penicillamine when compared with follow-up BPb and ZnP in children who were not chelated. Markowitz et al[8] observed a 2.5-μg/dL reduction in BPb during 7 weeks in children with BPb between 1.21 and 2.66 μmol/L after environmental remediation alone, which is fourfold to fivefold less than that observed in our study during a similar time span. Also, in the study by Markowitz et al,[8] changes in BPb and erythrocyte protoporphyrin concentration were not related to iron status or reducing exposure to lead-based paint, which further supports our opinion that DMSA therapy contributed significantly to the fall in ZnP.

The setting of our study could have biased the results against a favorable response. Our patients were treated as outpatients, a setting in which compliance with taking medication could not be ensured and in which continued exposure to low doses of lead was probable. Despite these limitations, no patient had a significant increase in BPb, and no patient had an increased ZnP.

Because pretreatment BPb were obtained on the average of 8 days before commencing DMSA therapy, our results may have been biased by possible fluctuations in BPb that might have occurred shortly before initiating chelation therapy. Because the direction of flux is not predictable, it is unknown whether this would bias the results in favor of a response to therapy or against it.

It is interesting to speculate on why all patients did not respond to DMSA. The nonresponders tended to have a smaller change in BPb during therapy, suggesting ongoing exposure, noncompliance, decreased absorption of DMSA or a suboptimal response to DMSA. It is also possible that changes in BPb may be inversely related to the body burden of lead. This is purely speculative, because our study did not measure total body lead stores.

In the past, children who have undergone chelation therapy for BPb of less than 2.17 μmol/L have received parenteral EDTA or oral D-penicillamine. The efficacy of EDTA in this range is modest at best,[4,8] with postrebound BPb approximately 10% to 20% lower than pretreatment values. It is also expensive, because it involves a 5-day hospitalization. Penicillamine has been used as an oral lead chelator for more than 25 years but is not approved by the Food and Drug Administration for this indication. Its efficacy is modest (18% reduction in BPb after rebound), and adverse reactions are common (33% incidence).[2] The findings of our study and that of Liebelt et al[6] support the use of oral, outpatient DMSA as an effective alternative to EDTA or penicillamine chelation in children with BPb of 2.36 μmol/L or less.

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