Effects of Calcium Disodium Versenate ($CaNa_2EDTA$) Chelation in Moderate Childhood Lead Poisoning

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ABSTRACT. *Background.* **For children with asymptomatic moderate lead poisoning (Blood lead level [BPb] 25 to 55 μg/dL [1.21 to 2.66 μmol/L]), treatment with the chelating agent calcium disodium versenate ($CaNa_2EDTA$) is recommended for all those children with a BPb level >45 μg/dL (2.17 μmol/L) and for those with a BPb level of 25 to 44 μg/dL (1.21 to 2.13 μmol/L) who also have a positive lead mobilization test. However, controlled studies demonstrating its efficacy at inducing a sustained reduction in BPb level or lead-related toxicity have not been performed in children with moderate lead poisoning. This study assesses the relationship between $CaNa_2EDTA$ chelation and measures of lead burden and toxicity in children with moderate lead poisoning.**

Methods. **Two hundred one children with moderate lead poisoning were enrolled. Sequential changes in BPb concentrations, bone lead level as measured by Lα-x-ray fluorescence, and lead-induced toxicity as assessed by erythrocyte protoporphyrin levels were determined over a 7-week period. From this group, children with a positive lead mobilization test received $CaNa_2EDTA$ chelation therapy.**

Results. **Children with positive lead mobilization tests had on average higher initial BPb, bone lead, and erythrocyte protoporphyrin concentrations. The chelated children decreased approximately 4.7 μg/dL (0.23 μmol/L), 41 corrected net counts, and 24 μg/dL (0.46 μmol/L) more than the unchelated children on BPb, bone lead, and erythrocyte protoporphyrin values, respectively. However, children with higher initial levels decreased the most, whereas children with lower initial levels showed the least decline, with or without treatment. When the initial values on the measures were controlled analytically, or when subgroups matched on initial levels were compared, there were no significant differences between the chelated and unchelated children.**

Conclusions. **The apparent effectiveness of $CaNa_2EDTA$ at reducing lead burden and toxicity is no longer observed when the pretreatment levels are considered. The findings suggest that sufficient doubt about $CaNa_2EDTA$ efficacy now exists to warrant a randomized controlled trial of chelation therapy in moderately lead-poisoned children. However, until such studies are performed, it would be premature to withhold chelation treatment on the basis of this study alone.** ***Pediatrics* 1993;92:265–271; *lead poisoning, chelation therapy, erythrocyte protoporphyrin, x-ray fluorescence.***

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ABBREVIATIONS. $CaNa_2EDTA$, calcium disodium versenate; BPb, blood lead; LMT, lead mobilization test; EP, erythrocyte protoporphyrin; LXRF, Lα-x-ray fluorescence; CNET, corrected net counts; HES, home environment scale.

The introduction of chelation therapy in the 1940s for the management of symptomatic lead poisoning resulted in decreased mortality.[1] The combined use of the chelating agents British Antilewisite and calcium disodium versenate ($CaNa_2EDTA$) further improved outcomes.[2] From the 1960s onward, the institution of mass screening of high-risk children, coupled with the reduction in allowable concentrations of lead in household paints, markedly reduced the incidence of symptomatic lead poisoning.[3–5] Currently, most lead-poisoned children have blood lead (BPb) levels <55 μg/dL (2.66 μmol/L) and are asymptomatic.[6]

Moderately elevated BPb concentrations (25 to 55 μg/dL [1.21 to 2.66 μmol/L]) are associated with neurobehavioral deficits and biochemical toxicity.[6–10] Acutely lowering BPb levels by chelation therapy with $CaNa_2EDTA$ leads to prompt reversal of at least the biochemical toxicity.[11–13] However, the improvement in biochemical markers may be short-lived; BPb levels rebound in most children within days of completion of a treatment course.[12–15] During this period, lead is likely to be redistributed from skeletal stores to blood and soft tissues.

To date, controlled studies have not been performed to evaluate the efficacy of $CaNa_2EDTA$ at producing a significant and sustained reduction in lead burden and toxicity in asymptomatic lead-poisoned children. Nevertheless, the Centers for Disease Control have recommended that children with BPb ≥45 μg/dL (2.17 μmol/L) be chelated immediately and that those with BPb 25 to 44 μg/dL (1.21 to 2.13 μmol/L) be chelated based on a positive result of a $CaNa_2EDTA$ lead mobilization test (LMT).[6] Extrapolation from the observed beneficial effects of this drug in severely lead-poisoned children formed a significant part of the basis for these recommendations. The expectation of $CaNa_2EDTA$ effectiveness precluded the ethical construction of a randomized controlled study that would include a treatment-eligible but not chelated group of asymptomatic children.[16–18]

The primary purpose of this study was to assess the effect of $CaNa_2EDTA$ chelation in children with

moderate lead poisoning. This was carried out by comparing changes in BPb concentrations and other measures of lead burden and toxicity sequentially over a 7-week period of time in chelated and unchelated children. Both groups had comparable ranges in BPb concentrations; treatment assignment was based on the outcome of the LMT. A secondary purpose was to assess the contribution of changes in iron status, bone lead stores and the amount of leaded paint in the homes of the children to changes in BPb and erythrocyte protoporphyrin (EP) concentrations.

METHODS

The data for these analyses came from a study designed to assess the short-term (6 to 7 weeks) and long-term (6 months) effects of chelation treatment employing $CaNa_2EDTA$ in 5-day courses on cognitive and behavioral outcomes in moderately lead-poisoned children. Six weeks was considered to be a sufficient period of time for stabilization of BPb levels after perturbation by chelation (the "rebound phenomenon").[3,15,18]

Children, 1 to 7 years of age, who were referred to the Montefiore Medical Center Lead Clinic for the evaluation of plumbism were eligible for this study if they had not been treated previously and if the BPb levels were between 25 and 55 μg/dL (1.21 and 2.66 μmol/L) and EP levels ≥35 μg/dL (0.66 μmol/L). Two hundred one children were enrolled. Data from 174 subjects were used for analyses. Twenty-seven cases were excluded for the following reasons: BPb concentration >55 μg/dL (2.66 μmol/L) during the time period of study (n = 3), patient noncompliance (n = 20), extended interval between evaluations (greater than 8 weeks) (n = 3), and intercurrent illness that required hospitalization (n = 1). All children received an LMT, which was administered within 2 weeks of enrollment. Details of the test and its interpretation have been published elsewhere.[19] In brief, the LMT consists of a single intramuscular injection of $CaNa_2EDTA$, 500 mg/m^2, followed by an 8-hour urine collection for lead determination. If the ratio of total urine lead excreted (in micrograms) divided by the dose of $CaNa_2EDTA$ administered (in milligrams) yielded a value ≥0.6 for children younger than 36 months of age, or ≥0.7 for children older than 36 months of age, this was considered a positive LMT.[14] In addition, urinary lead excretion of ≥200 μg/vol (0.97 μmol/vol) was considered a positive LMT. Children with negative LMTs constituted the comparison group. Blood samples for lead, EP, and ferritin determinations were obtained immediately before the administration of the drug. The results of these blood tests were used in the current analyses.

During the week prior to the LMT, bone lead measurements were obtained noninvasively by Lα-x-ray fluorescence (LXRF).[20–25] This method employs an instrument that directs partially polarized photons at the medial midtibia.[20] The effective dose of a single LXRF procedure over a 16.5-minute period is calculated to be less than 3 μSv, about ½₀th of that for one dental x-ray.[20,21] An LXRF spectrum analyzer collects and counts photons in the 10.5 keV lead L region.[20–25] The net counts (L peak minus background) are corrected for the day-to-day variability of the instrument; and the net counts of the subject are divided by the net counts of a single bone phantom measured on the same day. The quotient is multiplied by a constant, representing averaged bone phantom readings derived from a reference time period.[20] This product is expressed as corrected net counts (CNET). A standard deviation of 10 CNET was calculated from replicate measurements of 37 lead paint-poisoned children at different tibial sites.[25] The correlation between these replicates was .984.[25] The coefficient of variation of multiple measurements performed on the same day using the bone phantom averaged 4%. Further details of this method have been published elsewhere.[20–25]

The homes of all the children were inspected to determine the degree of exposure to leaded paint. At the home visit, each surface was visually rated on a scale of 0 to 3 for the degree of peeling: 0 = intact wall and 3 = peeling. Ratings of 1 and 2 reflected bubbling or cracking of painted surfaces without overt evidence of peeling. All surfaces were then assessed in situ for their lead content by an XK3 x-ray fluorescence lead paint analyzer. The product of the XK3 readings and the visual inspection scores were summed for all surfaces in the entire home to yield the home environment scale (HES).

Children with positive LMTs were admitted to the hospital and received 5 days of $CaNa_2EDTA$ therapy, 1 g/m^2 daily, intravenously, divided in four doses.[6,14] Hospitalized children were discharged either to their repaired homes or to an alternative residence deemed lead-free by the Department of Health. The Department of Health followed a regimen similar to ours: visual inspection and XRF measurements. Landlords were notified of housing code violations. In general, dust and water lead content were not determined. The same process of inspection and repair was instituted for children with negative LMTs who were not treated with $CaNa_2EDTA$.

Six to 7 weeks after the initial evaluation, blood analyses were repeated, as were the bone lead measurements and home inspections.

Blood lead level was measured by graphite furnace atomic absorption spectrophotometry and EP was determined by the ethyl acetate/acetic acid extraction method.[26,27] The 95% confidence limits of the methods were 1 and <1 μg/dL (0.05 and <0.02 μmol/L), respectively. Serum ferritin level was determined by radioimmunoassay.[28] The intraassay and interassay coefficients of variation were 3% and 4%, respectively. A ferritin level greater than 15 ng/mL was considered evidence of iron sufficiency in the absence of any clinical evidence of inflammation. Iron-deficient children were prescribed therapeutic doses of iron (6 mg/kg daily).

Statistics. A variety of statistical strategies have been employed to analyze change over time in nonequivalent groups.[29–33] Three analytic approaches were chosen to assess the effectiveness of $CaNa_2EDTA$ therapy: (1) regression of the simple difference from time 1 to time 2 on treatment in the entire sample; (2) a multiple regression of the difference between time 1 and time 2 measures on treatment with the initial value covaried; and (3) regression of the simple difference on treatment in a subsample matched on initial value of the dependent variable—BPb (matched within 1 μg/dL (0.005 μmol/L), EP (matched within 5 μg/dL (0.095 μmol/L), or bone lead (matched within 10 CNET). The latter approach simulates an experiment in which subjects are matched on key variables and then randomized into treatment groups. Because the unchelated children had lower BPb, bone lead, and EP levels than the chelated group, this analysis was restricted to subjects with BPb values below 46 μg/dL (2.22 μmol/L), bone lead values below 286 CNET, and EP values below 190 μg/dL (3.60 μmol/L). A significance level of .05 was used as a criterion for the three tests of the effect of treatment. The assumption of parallel regression lines of change on initial value for the second analytic strategy was tested by inclusion of a term representing the interaction of treatment and initial value.

Twenty-two variables were assessed as potential confounders, suppressors, and moderators of the relationship between treatment, BPb, and EP. These included age of the child represented by linear and quadratic terms, iron status, bone lead, HES, and a number of sociodemographic variables such as a measure of socioeconomic status (Hollingshead Four-Factor Index), birth order, size of family, and the Caldwell Home Observation for Measurement of the Environment (HOME) Assessment scale.[34] Any variables associated at the .20 level of significance or less with both the outcome measure and treatment were added to specific analyses to assess whether the observed relationships were confounded or suppressed by the covariates.[35] Although there were substantial differences between the treatment groups of many of the potential covariates, only three were associated with treatment and the biochemical outcomes: estimated gestational age, household size, and mother's marital status. Control of the covariates did not substantially change any of the observed associations nor change statistical inferences. Therefore, the results presented herein do not include any of the covariates.

In addition to the central tests of the effectiveness of $CaNa_2EDTA$ therapy, a series of analyses were performed to test the effect of change in HES and iron status on change from time 1 to time 2 in BPb and EP. For those analyses employing iron status, children were categorized as deficient at both time points; deficient at time 1, sufficient at time 2; sufficient at time 1, deficient at time 2; or sufficient at both time points. Changes in BPb and EP were regressed on variables representing chelation treatment, change in HES, and change in iron status after the initial value had been entered. Missing data were replaced by group means in the

final model. The significance criterion used for these analyses was .01, due to the large number of analyses and their exploratory nature.

All the continuous variables were examined initially for kurtosis and skewness. Several transformations were made of the markedly nonnormal variables; and the transformation that resulted in the closest approximation of a normal distribution were used in the models. The variables were transformed by obtaining the natural logarithm of EP and HES and the square root of bone lead level. All statistical analyses employed the transformed variables; however, for ease of interpretation, the mean change reported in the tables and the data points in the figures are shown in the original metrics.

RESULTS

The sex and race distributions of the two treatment groups were similar. However, children who were treated with $CaNa_2EDTA$ were significantly older than the unchelated children (Table 1). At the beginning of the study (time 1), the children who were treated with $CaNa_2EDTA$ had significantly higher levels of BPb, bone lead, EP, and, by design, urine lead than the unchelated children. A greater proportion of the unchelated children were iron deficient at the beginning of the study. Although the chelated children had higher HES at time 1, the difference in log HES between the groups was not statistically significant.

Blood lead levels, EP levels, and HES declined significantly from time 1 to time 2 in the chelated and unchelated groups. Bone lead level declined significantly only in the chelated group.

TABLE 1. Description of Demographic, Biochemical, and Environmental Measures at Time 1*

	EDTA Treated (n = 71)	EDTA Untreated (n = 103)	*P*
Sex			
% Male	52.2	59.2	.45
% Female	47.8	40.8	
Race			
% Black	41.8	34.7	.33
% Hispanic	55.2	57.4	
% Other	3.0	7.9	
Age, mo			
Mean	39.6	31.2	.0002
SD	16.4	12.8	
Blood Pb, μg/dL†			
Mean	37.3	29.0	.0000
SD	8.1	5.6	
EP, μg/dL†			
Mean	143.3	78.0	.0000‡
SD	88.0	43.2	
Bone Pb, CNET			
Mean	191.4	125.3	.0000§
SD	105.4	87.1	
HES, U			
Mean	164.4	110.6	.207‖
SD	193.8	153.3	
Iron status			
% Deficient	31.9	48.0	.0534
% Sufficient	68.1	52.0	

* Abbreviations: EDTA ($CaNa_2EDTA$), calcium disodium versenate; EP, erythrocyte protoporphyrin; HES, home environment scale; CNET, corrected net counts.
† To convert from micrograms per deciliter to micromoles per liter, divide Pb by 20.7 and EP by 52.7.
‡ Test done after natural log transformation of EP.
§ Test done after square root transformation of CNET.
‖ Test done after natural log transformation of HES.

The raw change in levels of BPb, bone lead, and EP was significantly associated with treatment (Table 2). The chelated children decreased approximately 4.75 μg/dL (0.23 μmol/L), 41 CNET, and 24 μg/dL (0.46 μmol/L) more than the unchelated children on BPb, bone lead, and EP, respectively.

The changes in BPb and bone lead levels were strongly related to their initial values (Figs 1 and 2). Children with higher levels decreased the most, while children with lower levels showed the least decline, regardless of treatment group. The slopes of the regression lines of BPb change and bone lead change on the initial values in the two treatment groups were statistically indistinguishable (BPb $b_{rx \text{ by BPb time 1}} = -.18$, $P = .14$; bone Pb $b_{rx \text{ by bone Pb time 1}} = .21$, $P = .28$). The lack of significant interactions between treatment and the initial level of BPb or bone lead indicates that treatment was neither more nor less effective for those who started out with larger lead burdens. When the initial BPb and bone lead values were controlled analytically, there were no significant differences between change in BPb or bone lead in the chelated and unchelated children (Table 2). After taking the initial values into account, the chelated children decreased 0.06 μmol/L (1.2 μg/dL) more than the unchelated in BPb and 8.1 CNET less in bone lead.

The relationship between the initial EP value and subsequent change differed in the two treatment groups as evidenced by a statistically significant interaction between treatment and initial level of EP (Fig 3) ($b_{rx \text{ by EP time 1}} = .17$, $P < .02$). The relationship between initial level and change was stronger in the unchelated children than in the chelated group. This conditional relationship is due in part to a small number of chelated children with the lowest initial EP levels whose EP levels declined more than would be expected on the basis of their relatively low initial values. When two of these cases were deleted from the analysis, the treatment by initial EP interaction ceased to be statistically significant at the .05 level ($b_{rx \text{ by EP time 1}} = .13$, $P = .10$). Due to the interaction between treatment and initial level of EP, the test of the effect of treatment could not be simply adjusted for initial level of EP. Instead, the children were stratified into those above and below the median on initial EP. While treatment had a larger effect on decreasing EP in those at or below the median in initial EP ($b_{rx} = -.10$, $P = .21$) than in those above the median ($b_{rx} = -.04$, $P = .48$), treatment was not significantly related to change in EP in either those above or below the median in initial EP.

When the analysis was restricted to chelated and unchelated groups who were matched on initial value of the variable (Table 2), there was also no significant difference between change in BPb, bone lead, or EP value in the two groups.

A second set of analyses was conducted to evaluate three factors other than chelation treatment which may have contributed to or explained the observed changes in BPb and EP: changes in HES, iron status, and bone lead level. For these analyses, bone lead level was conceptualized as a predictor of change in BPb, as a decrease in BPb could reflect a shift of lead

TABLE 2. Mean Change* (Time 2 Minus Time 1) in Blood Lead, Bone Lead, and Erythrocyte Protoporphyrin (EP) Levels by Chelation Treatment

	Blood Pb, μg/dL			Bone Pb, CNET			EP, μg/dL		
	No Rx	Rx	*P*	No Rx	Rx	*P*‡	No Rx	Rx	*P*§
Raw change (full sample)	−2.5	−7.2	<.001	−3.3	−44.9	<.001	−12.6	−37.4	<.001
Adjusted for initial levels†	−3.9	−5.2	.21	−23.9	−15.8	.86	. . .‖		
Raw change¶ (sample matched on initial level)	−4.1	−5.8	.23	−12.9	−12.1	.89	−25.8	−25.3	.33

* The mean changes in blood lead, bone lead, and EP concentration are shown in their original metrics; the significance tests shown are of the square root transformation of bone lead and the natural logarithmic transformation of EP. To convert from micrograms per deciliter to micromoles per liter, divide lead by 20.7 and EP by 52.7. CNET, corrected net counts.
† Change was evaluated at the mean of time 1 measures in the sample.
‡ *P* is the significance of statistical tests using the square root transformation of bone lead.
§ *P* is the significance of statistical tests using the natural logarithmic transformation of EP.
‖ Analysis of covariance was not performed because of a statistically significant treatment by initial EP interaction (see text).
¶ Subjects from the chelated and nonchelated groups were paired based on matching of initial values for each variable of interest.

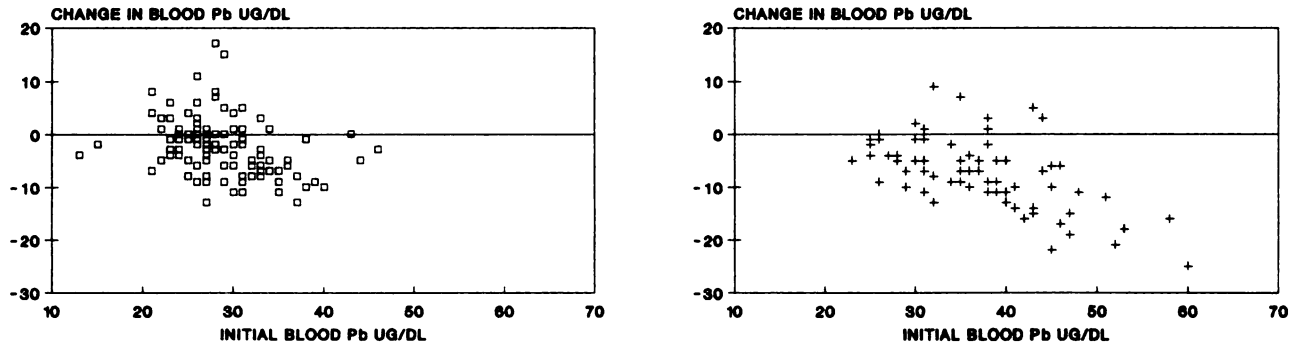

Fig 1. Change in blood lead level vs initial blood lead level: comparison of chelated and unchelated groups. The initial time point values given on the horizontal axis are plotted vs the change in the measure on the vertical axis. Change in the measure equals time 2 minus time 1. □, Unchelated; +, chelated.

from soft to hard tissues. Alternatively, a failure of BPb to decrease could be due to a shift of lead from bone to blood. Changes in BPb and EP were unrelated to change in any of these factors (HES, iron status, bone lead level) both with and without the initial level of BPb and EP controlled. There were also no significant interactions between treatment and change in HES, bone lead level, and iron status, indicating that the effect of treatment was not conditional on change in any of these factors. The combined effect of chelation treatment, iron supplementation, and environmental lead abatement accounted for 4.9% more variance in BPb change than initial BPb level alone ($P = .05$), which by itself accounted for 31.9% of the variance in BPb change. Similarly, all three treatment modalities accounted for 4.1% more variance in EP change than initial EP level alone ($P = .23$), which accounted for 13.3% of the variance in EP change.

DISCUSSION

Asymptomatic childhood lead poisoning is currently the most common environmentally produced disease, with toxicity demonstrated by abnormalities in biochemical, anthropometric and neurobehavioral measures.[5–7,9,36] Clinical intervention involves several approaches: (1) identification and eradication of the environmental lead source; (2) nutritional counseling to reduce lead absorption and retention; and (3) drug therapy to enhance lead removal from the body.

Leaded paint in the primary residence is overwhelmingly the source of ingested lead in urban American children.[10] The number of households with young children at risk from leaded paint has been estimated at nearly 4 million.[37] Of the children in this study, 89% had leaded paint contamination of their houses at the time of clinic referral. Intensive efforts at reducing exposure to this source were partially successful. Average HES declined from 129 to 82 from time 1 to 2; however, 79% of the primary residences still had an HES greater than 0 at time 2. Efforts at reducing environmental lead have been reported to correlate with a decline in BPb concentrations.[38] In this study, regression analyses failed to show a significant relationship between reduction in household exposure to reduction in BPb. A direct comparison between our study and the previous report cannot be made since the aim of our home intervention was the abatement of lead hazards by compliance with existing housing codes, not dust control measures as delineated in the previous study.[38]

The association of nutritional mineral deficiencies and increased lead absorption and retention has also been demonstrated.[7] In particular, iron deficiency is

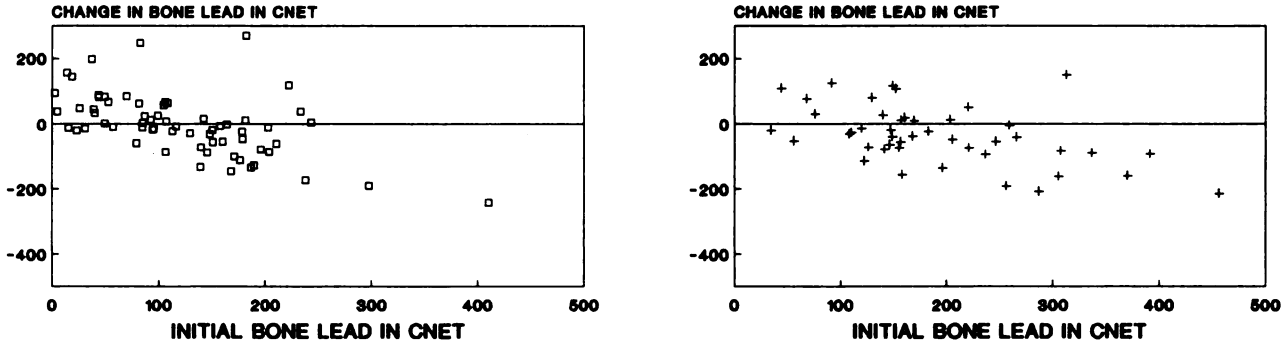

Fig 2. Change in bone lead level vs initial bone lead level: comparison of chelated and unchelated groups. The initial time point values given on the horizontal axis are plotted vs the change in the measure on the vertical axis. Change in the measure equals time 2 minus time 1. □, Unchelated; +, chelated. CNET, corrected net counts.

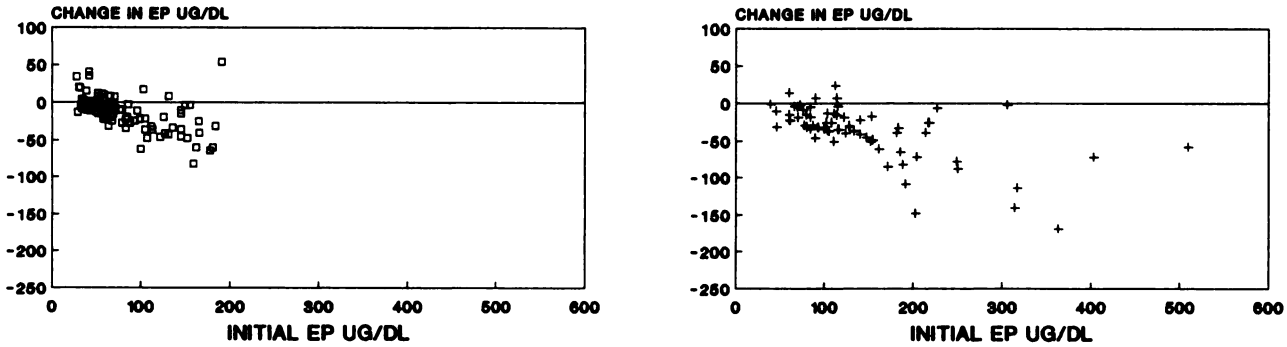

Fig 3. Change in erythrocyte protoporphyrin (EP) level vs initial EP level: comparison of chelated and unchelated groups. The initial time point values given on the horizontal axis are plotted vs the change in the measure on the vertical axis. Change in the measure equals time 2 minus time 1. □, Unchelated; +, chelated.

frequently observed in lead-poisoned children.[39] Iron deficiency is associated with enhanced lead absorption and may also inhibit the effectiveness of $CaNa_2EDTA$ at inducing a maximal lead diuresis.[28,39] Nearly half of the patients in this study had low serum ferritin levels at enrollment. Most of those children were still iron deficient by the second time point. The change in iron status, when it occurred, did not contribute significantly to the reduction in observed BPb levels.

In children who have markedly elevated BPb concentrations (>2.17 μmol/L [45 μg/dL]) or positive mobilization tests, the administration of a chelating agent such as $CaNa_2EDTA$ increases the rate of urinary lead excretion up to tenfold during the course of treatment. The source of this lead is hard and soft tissues.[6,40–42] In the present study, tibial bone lead level, as assessed by LXRF, declined on average in the $CaNa_2EDTA$ chelated group only. However, when the initial bone lead level was controlled in the statistical analysis, this effect of treatment was no longer evident (Table 2). Thus, the magnitude of the decline in bone lead is dependent on the amount of bone lead at enrollment. The greater the initial bone lead value, the greater the fall after 7 weeks, irrespective of chelation treatment.

Similarly, the effect of $CaNa_2EDTA$ chelation on the change in BPb concentrations over the period of observation was not clear-cut. Namely, the apparent effect of chelation therapy on BPb level reduction, present in the analysis of raw change, could be accounted for by the higher initial BPb concentrations in this group compared with the unchelated group. Once the difference between the initial BPb levels was controlled analytically, the differences between groups disappeared. This was most clearly demonstrated when the groups were matched on initial BPb level. A difference between the groups could not be discerned.

While $CaNa_2EDTA$ chelation therapy promptly lowers BPb concentrations, our findings suggest that the effect may not be sustained over time. Other investigators have made similar observations. Hryhorczuk et al[43] studied the duration of the effect of chelation on BPb values in adult workers and found that after each course of treatment, the rebound in BPb levels approached prechelation values beginning 7 days posttreatment. Moel et al[18] followed a group of severely lead-poisoned children (initial BPb >100 μg/dL [>4.83 μmol/L]) for at least 10 years and also found no relationship between number of courses of chelation given and eventual BPb level. Although these studies are not comparable with ours in population, time frame of follow-up, or control for initial BPb values, both are suggestive of a limited effect of $CaNa_2EDTA$ therapy.

In the absence of chelation, the half-life of lead in the blood of excessively exposed adults is weeks to years.[43–45] During experimental acute ingestion of stable lead isotopes by normally exposed volunteers, Rabinowitz et al[46] found the elimination half-life of BPb to be 4 to 6 weeks; however, day-to-day BPb levels could vary by ±10%.[47]

Although comparable experimental studies employing known quantities of lead have not been performed in children, three groups have observed the natural decline in BPb concentrations in unchelated, moderately lead-poisoned children.[17,48,49] In general, the findings of these studies are compatible with ours: (1) BPb levels decline over time in the absence of chelation, and (2) the higher the initial BPb level, the greater the reduction: 59 to 46, 51 to 45, 48 to 45 μg/dL (2.85 to 2.22, 2.46 to 2.17, and 2.32 to 2.17 μmol/L, respectively).[48,17,49]

If there was no definitive effect of $CaNa_2EDTA$ chelation on BPb level, was there an improvement in biochemical toxicity? Here again, the decline in EP levels was related to chelation treatment in the raw bivariate analysis, ie, chelated children had a significantly greater decline in EP values. However, a significant interaction between treatment group and initial EP level indicates that $CaNa_2EDTA$ treatment is not effective in children with high initial levels of EP. While the interaction suggests that chelation treatment may be more effective in those with the lowest initial EP values, it is based on a small group of children. Furthermore, the analysis of the samples matched on initial EP level supports the inference that $CaNa_2EDTA$ chelation treatment does not improve biochemical toxicity once initial level is taken into account.

Similarly, Hryhorczuk et al[50] failed to find a relationship between the fall of zinc protoporphyrin levels and the amount of $CaNa_2EDTA$ given to lead-exposed workers. We and others have also reported previously that initial improvement in aminolevulinic acid dehydratase activity diminished as BPb levels rebounded postchelation.[12,13]

The current study suggests that chelation treatment does not clearly account for the observed fall in blood or bone lead levels or in EP levels. Neither is the decrease in these measures solely accounted for by reduction in home lead exposure, iron supplementation, or, for BPb, by a shift of lead into bone. We must then consider the phenomenon of regression to the mean, the statistical expectation that individual scores which are far from the mean at one point in time will be closer to the mean at a subsequent time point. This phenomenon is thought to reflect chance variation in measurement and/or inherent instability over time. For example, high initial BPb values may reflect erroneously high readings due to measurement error, acute exposure, or random fluctuation of lead concentrations. Factors such as these would not be expected to occur again on subsequent measurements. Therefore, subjects with high initial values would be expected to have lower subsequent values even in the absence of treatment.

One additional explanation deserves consideration. Unquestionably, urinary lead excretion is increased during chelation treatment in LMT-positive children. However, this may represent only a small portion of the total amount of lead in the body, an amount that would have been excreted spontaneously, although at a slower rate. For example, if urinary lead during chelation is increased fivefold over spontaneous excretion and treatment is given for 5 days, then the equivalent of 25 days of spontaneous lead excretion is achieved during those 5 days. If this accelerated urinary lead diuresis results in a subsequent fall in spontaneous lead excretion for the 20 days following chelation, ie, until reequilibration from bone stores occurs, then no net gain from chelation would be visible 7 weeks later (as assessed in our study).

In summary, children treated with $CaNa_2EDTA$ did evidence significantly greater reductions in levels of BPb, bone lead, and EP from time 1 to time 2 than did the unchelated children (Table 2). However, because their initial values were higher compared with those of the unchelated children, it is unclear whether this difference between the groups of children is attributable to treatment. Both the analysis of covariance, which adjusted for initial level of the biochemical measures, and analysis of raw change in the subjects matched on initial level suggest that there is only a marginal difference in the decrease between the two groups. However, neither of these techniques allows safe inferences outside the range of the overlap of the initial values.

Our groups, while comparable on some measures such as BPb range, were not equivalent. While the relationship between change in the outcomes was parallel in both groups, it is still possible that chelation-eligible children would have shown less decrease in their time 2 values, or even an increase, if chelation had been withheld. Therefore, it would be premature to conclude that $CaNa_2EDTA$ chelation should be withheld from LMT-positive children. Our findings do suggest that there is now sufficient doubt about $CaNa_2EDTA$ efficacy to warrant a randomized controlled trial in moderately lead-poisoned children.

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. . . outsiders now frame the normative principles that guide the doctor-patient relationship. The critical pronouncements no longer originate in medical texts but in judicial decisions, bioethical treatises, and legislative resolutions. Outsiders, not doctors, define the moral codes that guide physician behavior.

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