0031-3998/00/4805-0593
PEDIATRIC RESEARCH

Vol. 48, No. 5, 2000
Printed in U.S.A.

Safety and Efficacy of Succimer in Toddlers with Blood Lead Levels of 20–44 μg/dL

TREATMENT OF LEAD-EXPOSED CHILDREN (TLC) TRIAL GROUP[1]

ABSTRACT

Although lead encephalopathy has virtually disappeared from the United States, thousands of children still have sufficient lead exposure to produce cognitive impairment. It is not known whether treating children with blood lead levels < 45 μg/dL (2.2 μM) is beneficial and can be done with acceptable safety. We conducted a 780-child, placebo-controlled, randomized trial of up to three courses of succimer in children with blood lead levels of 20–44 μg/dL (1.0–2.1 μM). Children were aged 12–33 mo, 77% were African-American, 7% were Hispanic, and they lived in deteriorating inner city housing. Placebo-treated children had a gradual decrease in blood lead level. Succimer-treated children had an abrupt drop in blood lead level, followed by rebound. The mean blood lead level of the succimer-treated children during the 6 mo after initiation of treatment was 4.5 μg/dL (95% confidence intervals, 3.7 to 5.3 μg/dL; 0.22 μM, 0.18 to 0.26 μM) lower than that of placebo-treated children. There were more scalp rashes in succimer-treated children (3.5% *versus* 1.3%) and an unanticipated excess of trauma. Succimer lowers blood lead level with few side effects. The unanticipated excess of trauma requires confirmation. **(*Pediatr Res* 48: 593–599, 2000)**

Abbreviations
CDC, Centers for Disease Control and Prevention
TLC, Treatment of Lead-Exposed Children
CI, confidence interval

Lead encephalopathy has virtually disappeared from the United States, and symptomatic lead poisoning has greatly decreased. Still, many children, especially those living in deteriorating housing (1), have sufficient lead exposure to produce cognitive impairment and perhaps also mild neurologic deficits and behavioral abnormalities. Their peak blood lead levels, which occur at 20 to 30 mo of age, are inversely associated with cognitive test scores measured at ages 4 to 10 y (2–6).

In 1991, the U.S. Food and Drug Administration licensed the first orally active lead chelator, dimercaptosuccinic acid or succimer, for the treatment of lead poisoning (blood lead level ≥ 45 μg/dL; 2.2 μM) in children (7). Succimer reduced blood lead levels as well as or better than parenteral EDTA in children with blood lead concentrations ≥ 30 μg/dL (1.4 μM) (8). Coincidentally, also in 1991, the CDC (9) recommended universal screening of children for elevated blood lead levels.

The combination of increased screening activity, the availability of an oral drug, and the lack of data showing efficacy of any form of therapy for prevention of cognitive impairment led to the initiation of a randomized clinical trial of succimer sponsored by the National Institute of Environmental Health Sciences and supported in part by the Office of Research on Minority Health of the National Institutes of Health. The trial was designed to test the hypothesis that children with moderate blood lead levels who were given succimer would have higher scores than children given placebo on a range of tests measuring cognition, behavior, and neuropsychological function 3 y after treatment. This paper presents the data on safety of succimer and its efficacy in lowering blood lead level.

METHODS

Centers. The TLC clinical sites were in Philadelphia, PA, U.S.A.; Newark, NJ, U.S.A.; Columbus/Cincinnati, OH, U.S.A.; and Baltimore, MD, U.S.A. All sites were already accepting referrals and caring for lead-poisoned children when TLC began. TLC operated on a common protocol for evaluating referred children, drawing and handling blood samples, randomization, drug treatment, and psychometric testing. Newark accepted Spanish-speaking families, and 39 (5% of TLC overall) children were identified by Newark staff as requiring assessment in Spanish at randomization. TLC had a common protocol for monitoring compliance, which consisted of diaries and pill counts, but the Cincinnati site used special bottles with computer chips in the caps in addition (data not shown here). All sites used the same basic house-cleaning protocol, but

Received February 15, 2000; accepted May 10, 2000.
Correspondence and reprint requests: Walter J. Rogan, M.D., Epidemiology Branch, National Institute of Environmental Health Sciences, P.O. Box 12233, Research Triangle Park, NC 27709, U.S.A.
Supported by National Institute of Environmental Health Sciences Contracts and Intra-Agency Agreements in cooperation with the Office of Research on Minority Health, NIH.
[1]Members of the TLC Trial Group are listed in the Appendix.

varied in the degree to which they monitored lead in the house. Although recruitment and retention goals were the same for all sites, the procedures for attaining them were decided on by the individual sites. It was the intent of the TLC investigators to do a single trial with multiple sites, and variations that appeared to the steering committee to endanger that goal were not permitted.

Children. The TLC trial was approved by the institutional review boards at each of the clinical sites, the Harvard School of Public Health, the National Institute of Environmental Health Sciences, and CDC. Recruitment in TLC is described elsewhere (10). TLC accepted referral of children who were 12 to 33 mo of age, had a referral blood lead level between 20 and 44 μg/dL (1.0–2.1 μM), had no more than two residences where they spent more than 8 h a day on a regular basis, and to whom psychometric tests could be administered in English (or Spanish, in Newark). Informed consent (for prerandomization activities) was obtained at the first TLC clinic visit. We measured venous blood lead level, ferritin, blood counts, renal function, and serum enzymes. Ferritin and blood lead level were measured centrally at CDC. Each family was given a month's supply of TLC vitamin and mineral supplements, which included iron, zinc, calcium, and copper. TLC staff inspected the child's home to see whether the TLC cleaning regimen could be expected to suppress exposure to leaded dust.

Children with blood lead levels between 20 and 44 μg/dL (1.0–2.1 μM) in the blood sample drawn by TLC had a second visit. If the child was still eligible, a second blood sample was drawn for measurement of blood lead level. The child was assigned randomly to a treatment group, and a second consent form (for treatment and follow-up activities) was completed if the child's second blood lead level was also between 20 and 44 μg/dL (1.0–2.1 μM) and the child's home(s) met study criteria, or, in a few cases, if the family could move. The second blood lead level was used as the baseline value for evaluation of treatment effects. About half of the children referred to TLC were randomized (10); most disqualifications were because of a TLC blood lead level $<$ 20 μg/dL (1.0 μM).

Interventions. All families had their home(s) inspected. Before treatment with succimer or placebo began, 14 families were helped to move to more lead-safe housing, which had been built after 1978 or completely abated, or stayed in lead-safe temporary housing while their home was abated. All but 15 other homes were cleaned before treatment, which consisted of vacuuming and/or damp-mopping all accessible surfaces, using a high efficiency particulate arrestor (HEPA)-filtered vacuum cleaner and a phosphate detergent solution. If a family moved during or after treatment, their new home was inspected and cleaned, if necessary.

The vitamin and mineral supplements were discontinued once the child was randomly assigned to a treatment group, and then were begun again after the treatment period and continued through follow-up. The supplements that TLC dispensed from April to July 1997 were recalled because of lead contamination, but we could not detect any effect of the contamination on the children's blood lead levels (11).

Randomization. Detailed tables of the characteristics of the two randomized groups are given elsewhere (10). TLC treated 780 children: 396 in the succimer group and 384 in the placebo group. Treatment assignments were randomized within strata of the four clinical centers, six categories of body surface area, two strata of blood lead levels ($\leq$ 25 μg/dL, or $>$ 25 μg/dL (1.2 μM)) and, in Newark, English or Spanish language. In addition, variables that were balanced by randomization included age, sex, blood count and enzyme values, self-designated race, birth weight, and blood pressure.

Succimer and placebo. Succimer is produced as 100-mg Chemet capsules. McNeil Consumer Products (Fort Washington, PA, U.S.A.) provided unmarked Chemet and placebo capsules of identical appearance. Because succimer has a strong, sulfurous, mercaptan odor, we packed 200 mg of succimer in a vented plastic cylinder in each bottle of placebo and succimer. Although this did not provide the placebo bottles with the room-filling odor of succimer, it did give the placebo an obvious aroma. The labels had a scratch-off area that identified the contents as succimer or placebo in case of emergency. Families were told that capsules would be counted, and were given a medication diary.

The children were assigned to one of six dose regimens based on an estimate of body surface area. Dose regimens were designed to come as close as possible to the dose rate on the Chemet label without using fractions of capsules. Note that, although the Chemet label provides doses both by body surface area and by weight, young children such as the ones in TLC get much higher doses using the body surface area method (12). Details of dose are published (10) and are on the Web site (http://dir.niehs.nih.gov/direb/tlc1/treat/tables.htm).

Treatment courses were 26 d in length. Children could receive up to three courses of treatment. Children were scheduled to return for clinic visits at 7, 28, and 42 d after the beginning of each treatment course. If a child receiving succimer had a blood lead level of $\geq$ 15 μg/dL (0.7 μM) at the 6- to 8-wk follow-up visit of the first or second course (conducted at a median of 48 d, 5% to 95% range of 41 to 101 d for the first course, similarly for the second), an additional course of treatment was initiated. Of the children receiving succimer, 83% required retreatment after the first course, and 83% of those receiving a second course of treatment required a third (Table 1). Children given placebo were assigned to retreatment to match the frequency of retreatment of children given succimer within the blocks used in the initial randomization.

Chemet capsules are too large for small children to swallow, and staff instructed the parents on how to open the capsules and sprinkle the coated beads onto applesauce, juice, etc. All instructional capsules were placebos.

Safety monitoring. Succimer was prescribed under an investigational new drug permit, because TLC used the drug at lower than labeled blood lead levels and because the treatment courses were 1 wk longer than the labeled 19 d. Each clinician in TLC participated in annual site visits, in which the U.S. Food and Drug Administration definitions of adverse events and TLC reporting procedures were presented, along with a series of short fictional case studies.

At each of the treatment visits, the families were asked about nausea, vomiting, rashes, and other side effects that previously had been reported in children taking succimer. Blood lead

Table 1. *Number of children by treatment group, courses of succimer, percentage completing each course, and percentage requiring retreatment by baseline blood lead levels*

Treatment variable	Baseline blood lead level (μg/dL)				
	20–24	25–29	30–34	35–44	Total
Placebo					
Number of children	178	120	55	31	384
Succimer					
First course					
Number of children	181	112	60	43	396
% Completing course*	94%	89%	95%	93%	93%
% Requiring retreatment†	73%	90%	93%	100%	83%
% Off protocol‡	4%	2%	6%	5%	4%
Second course					
Number of children	119	88	50	38	295
% Completing course	94%	92%	94%	92%	93%
% Requiring retreatment	71%	85%	91%	100%	83%
% Off protocol	4%	6%	2%	0%	4%
Third course					
Number of children	77	65	42	35	219
% Completing course	82%	82%	88%	100%	86%
% Requiring retreatment	75%	75%	86%	94%	81%

* Completed course = percentage of children attending final visit of course (d 42).

† Requiring retreatment = percentage of children with blood lead level $>$ 15 μg/dL at d 42 clinic visit.

‡ Off protocol = percentage of children who required retreatment but who did not continue treatment.

Notes: To convert μg/dL to μM, multiply by 0.048.

Children who went off treatment protocol were still eligible to continue in other aspects of the study.

level, blood cell counts, and serum enzymes were measured. Abnormally high serum enzyme values were repeated. We also decided on a value constituting an adverse event for counting purposes. This was arbitrarily set at twice the local upper limit of normal for aspartate aminotransferase and alanine aminotransferase and 5 times the upper limit for alkaline phosphatase, because of the clinicians' experience of considerable unexplained variability in the latter serum enzyme. Because the laboratory values were potentially affected by succimer, a designated physician at each site who was not involved in the child's clinical care received the results of the laboratory tests and checked whether any result violated predetermined boundaries.

If a child's blood lead level increased by $>$ 15 μg/dL (0.7 μM), the Data Coordinating Center notified the clinical center to repeat the blood lead level. If the increase was confirmed, then an assessment of the child's home(s) was initiated. Similarly, if a child's blood lead level was between 45 and 59 μg/dL (2.2–2.8 μM), the Data Coordinating Center notified the clinical center to repeat the blood lead level. If the high blood lead level was confirmed, or if any blood lead level ever exceeded 60 μg/dL (2.9 μM), study treatment was interrupted, and the child was managed according to the clinical center's local standards of care.

Statistical Methods

Average posttreatment blood lead level was calculated for each child by the trapezoidal method. Specifically, sequential pairs of blood lead levels were connected by straight lines and the area under the resulting curve was divided by the duration of the interval (6 or 12 mo). Mean blood lead levels and 95% CI were calculated for each treatment group, and the difference in means was evaluated by the two-sample *t* test.

To generate smooth curves of blood lead level *versus* time for the succimer and placebo groups, treatment- and time-specific means were calculated by locally weighted regression (13, 14), using S-Plus software (15). This method makes no assumptions about the functional form of the relationship between group mean and time after randomization. The estimate of the average blood lead level at any given time is the weighted mean of the observed blood lead levels measured in the neighborhood around that time. The size of the neighborhood is defined by the span parameter, which for these analyses was 0.3 (see figures). An estimate and 95% confidence interval for the mean at each time point were calculated for each time point assuming a symmetric distribution of blood lead levels around the mean.

Tests for equality of the proportions of hospitalizations, children hospitalized, and children with reports of signs or symptoms in the two treatment groups, CI for differences in proportions, and power were calculated using exact methods implemented in StatXact software (Cytel Software Corporation, Cambridge, MA 02139, U.S.A.).

RESULTS

Completion and adherence. By the parents' reports, $>$ 90% of doses were given, and, by pill count, about 76% of the capsules were gone from the bottle. Twenty-six percent of the families given placebo and 40% of the families given succimer reported difficulty administering the drug. Interruptions in the administration of the drug were similar, 30% with succimer and 27% with placebo. Of those with interruptions, 39% of the children given succimer and 45% of the children given placebo resumed taking the study medication.

Blood lead level. Figure 1 shows mean blood lead levels by treatment group as a function of time. The largest difference of approximately 11 μg/dL (0.5 μM) occurs at 1 wk after beginning therapy. Rebound, presumably from stored lead, begins after 1 wk of treatment, and continues. At 7 wk after start of treatment, the children in the succimer group have blood lead levels 72% of baseline, whereas the children in the placebo group have 88% of baseline. Blood lead level again drops in the succimer group with the second and third courses of treatment (Fig. 2), and in each case rebounds. The placebo group had a gradual decline in average blood lead level. The mean blood lead level of the succimer group was 4.5 μg/dL (95% CI, 3.7 to 5.3 μg/dL; 0.22 μM, 0.18–0.26 μM) lower than that of the placebo group during the 6-mo period after initiation of treatment, and 2.7 μg/dL (95% CI, 1.9 to 3.5 μg/dL; 0.13 μM, 0.09–0.17 μM) lower during the 12-mo period after initiation of treatment. Splitting the data at 24 mo of age, median body surface area, by sex, by Spanish *versus* English language, or by center produces curves that are similar to those for all children.

The TLC criterion for retreatment was blood lead level $\geq$ 15 μg/dL (0.7 μM) at the scheduled d 42 follow-up for children

given succimer. Table 1 shows that for blood lead levels of 20–24 μg/dL (1.0–2.1 μM), 73% required further treatment after one course, and of those starting the second course of treatment, 71% required another course. All of the children with the highest initial blood lead levels (35–44 μg/dL; 1.7–2.1 μM) who completed treatment (35 of 43) required three courses of treatment.

Treatment-specific mean blood lead levels *versus* time were compared by number of courses of treatment received. Note that the placebo curves for Figure 2 are for children who received one, two, or three courses, but this assignment did not depend on persistently high blood lead levels as it did in the children given succimer. Rather, assignment to one, two, or three rounds among the children given placebo was stratified in the same way as the initial randomization. Thus, the children given one course of placebo had higher blood lead levels at baseline than the children who were given one course of succimer, but lower than those who received three. The mean blood lead level *versus* time for the children who received only one course of succimer was always less than that of the placebo-treated children (Fig. 2). Children who received two courses of succimer had lower mean blood lead levels than those who received placebo out to 52 wk after the beginning of treatment. Mean blood lead levels of the children who were given three courses of succimer was lower out to approximately 42 wk.

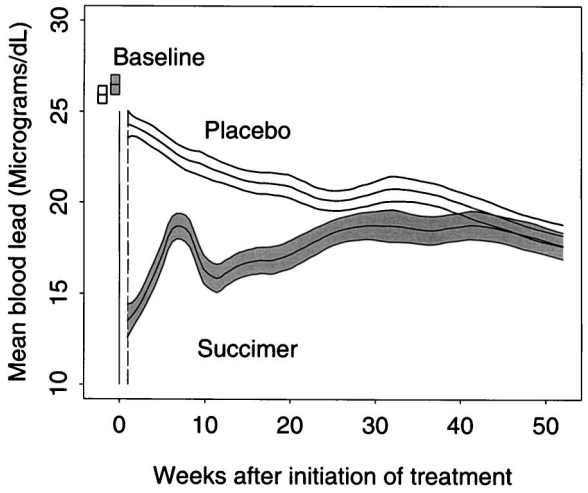

Figure 1. Mean blood lead level and 95% CI at baseline and by week after initiation of treatment for children in the succimer (shaded) and placebo groups. Means were calculated by locally weighted regression (span = 0.3). The hatched vertical line marks 1 wk after randomization, which is the first time blood lead level was measured after treatment was begun. To convert μg/dL to μM, multiply by 0.048.

Hospitalizations. We counted hospitalizations that occurred while the children were taking succimer or placebo and for 3 mo thereafter. There were 42 hospital admissions in 37 children. Twenty-two of the children given succimer were hospitalized 25 times *versus* 15 of the children given placebo, who were hospitalized 17 times (5.6% *versus* 3.9% of children; difference, 1.6%; 95% CI, −2.0 to 6.3%). Asthma or pneumonia and lead poisoning were the commonest reasons for hospitalization. The number of hospitalizations for asthma was the same, six (1.5% *versus* 1.6%) from each group, but seven children given succimer were hospitalized for lead poisoning *versus* four given placebo (1.8% *versus* 1.0%; difference, 0.7%; 95% CI, −1.7 to 4.3%). Five (1.3%) of the children given succimer and none of the children given placebo were hospitalized for trauma (difference, 1.3%; 95% CI, −0.5 to 4.3%). The reasons for hospitalization showed no pattern. There were two head injuries, a burn, a near-drowning, and a throat laceration. No child died.

Signs and symptoms. There were no statistically significant excesses of any adverse event in the succimer group. However, physical evidence of trauma was noted in 14.9% of those given succimer and 9.9% of those given placebo (difference, 5%; 95% CI, −0.1 to 11%). The caretaker noted hyperactivity or a synonym in 3.8% in those given succimer and 6% of those in the placebo group (difference, −2.2%; 95% CI, −7.0 to 1.5%), but irritability or a synonym was reported in 28.8% of those given succimer and 25% of those given placebo (difference, 3.8%; 95% CI, −2.8 to 10.9%). Of the hypothesized side effects, scalp rashes were reported in 3.2% of those given succimer and 1.3% of those given placebo (difference, 2.2%; 95% CI, −0.5 to 6.1%; Table 2).

Laboratory abnormalities. We anticipated that children taking succimer would have thrombocytopenia and decreased neutrophil counts, and, although both occurred more frequently

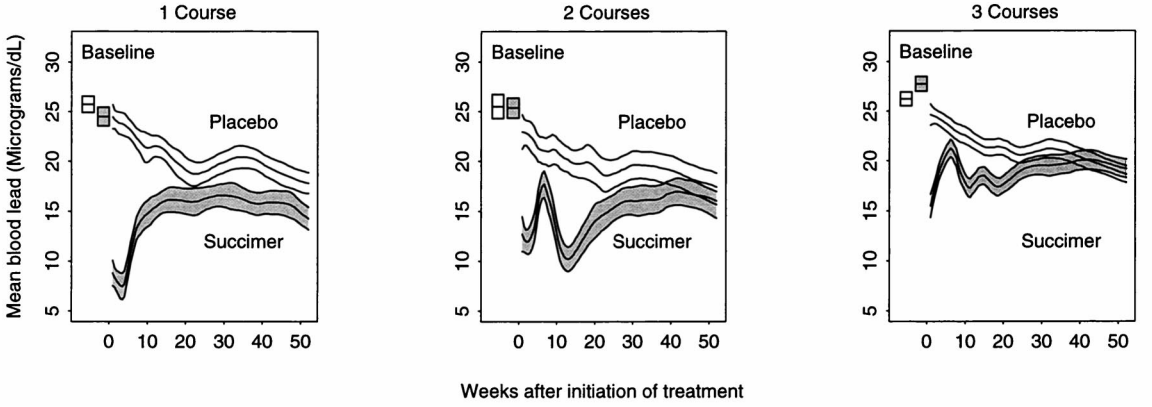

Figure 2. Mean blood lead level and 95% CI at baseline and by week after initiation of treatment for children in the succimer (shaded) and placebo groups, for children receiving one (n = 101 given succimer; n = 143 placebo), two (n = 76 succimer; n = 66 placebo), and three (n = 219 succimer; n = 175 placebo) courses of treatment. Means calculated by locally weighted regression (span = 0.3). To convert μg/dL to μM, multiply by 0.048.

in the succimer group, neither was statistically significant nor more frequent when the abnormal value was repeated (Table 3). The anticipated difference in alkaline phosphatase did not appear, and although the chance of having one abnormal alanine aminotransferase was twice as high in the succimer group, the difference was small and not statistically significant when the test was repeated.

DISCUSSION

Lead exposure is preventable, but, given the current prevalence of lead paint and leaded dust in the inner city housing stock, practical, effective means of managing lead-exposed children are needed. The other randomized trial of succimer (16) showed a small reduction in the blood lead level of children given one course of succimer compared with placebo at 1 mo of follow-up, and a slight increase at 6 mo of follow-up. That trial was very small ($n = 39$ children), and consequently its estimate of the size of the effect is unstable. TLC, a formal trial with intense involvement of the families, home clean-up, high doses of drug, and monitored adherence, represents the best that can be done practically with oral chelation in young children from poor families. In this trial, succimer produced a mean difference from placebo of 4.5 μg/dL (0.22 μM) blood lead level during 6 mo, and 2.7 μg/dL (0.13 μM) during 12 mo. There were not large differences in response to the drug by sex, site, language, body surface area, or age. TLC did not assess diet. We plan to perform analyses by compliance and by various measures of dust exposure, but these are secondary analyses and do not have the same interpretability as the comparisons that arise directly from randomization and intent-to-treat analyses that are presented here.

TLC is a too small a trial to establish safety. For a trial the size of TLC, an event with a frequency of 1% in the placebo group would have to increase to 4.2% to be detected with 80% power; 5% in the placebo group to 10.4%; 50% in the placebo group to 60.2% (by Fisher's two-sided exact test). TLC is, however, not a small trial, and we saw little evidence of toxicity with the intense TLC succimer regimen. Although there is a difference in hospitalization rates for treatment of lead poisoning, this is an artifact of clinical practice in TLC. Any child whose blood lead level was > 44 μg/dL (2.1 μM) was treated. Children who were taking succimer when this happened were admitted for chelation with EDTA. Most children receiving placebo were given succimer and managed as outpatients. There were seven children who were receiving placebo when their blood lead level was > 44 μg/dL (2.1 μM), of whom four were hospitalized, and 10 children taking succimer, nine of whom were hospitalized. Thus, it does not appear that succimer either prevents or causes episodes of increased lead absorption.

We have no explanation for the more frequent occurrence of trauma in the children given succimer. The excess is present both in hospitalizations and in the data from the histories and physicals. There is no common site or mechanism of injury. We did not gather detailed data about trauma, because we had no prior hypothesis about it. We see no obvious difference in the reported behavior of the children.

If succimer is to be used widely in children, research into alternate ways to administer it is needed. Of the families on placebo, 26% complained of difficulty with administration, including refusal by the child, perhaps because they had to open the capsules and sprinkle the contents. However, 40% of the families taking succimer had difficulty, with the additional 14% likely because of the odor of the drug.

Observational data suggest that the effect on IQ of an increase in blood lead level from 10 to 20 μg/dL (0.5–1.0 μM)

Table 2. *Reported signs and symptoms during treatment for children in the placebo and succimer groups**

		Placebo ($n = 384$)		Succimer ($n = 396$)		Difference in proportion (succimer − placebo)
Class	Sign or symptom	No.	Proportion (95% CI)	No.	Proportion (95% CI)	Difference (95% CI)
Gastrointestinal	Diarrhea	176	45.8 (40.8,51.0)	187	47.2 (42.2,52.2)	1.4 (−5.7,8.7)
	Vomiting	95	24.7 (20.6,29.2)	100	25.2 (21.1,29.7)	0.5 (−6.0,7.6)
	Abdominal pain	57	14.8 (11.4,18.7)	60	15.2 (11.8,18.9)	0.3 (−5.2,6.7)
	Nausea	33	8.6 (6.0,11.7)	31	7.8 (5.4,10.9)	−0.8 (−6.3,3.7)
Respiratory	Upper respiratory infection	170	44.3 (39.2,49.3)	187	47.2 (42.2,52.2)	3.0 (−4.1,10.3)
	Otitis media	50	13.0 (10.0,16.6)	52	13.1 (10.0,16.8)	0.1 (−5.2,6.3)
	Asthma	21	5.5 (3.5,8.2)	27	6.8 (4.5,9.7)	1.3 (−2.6,6.4)
Dermatologic	Rashes on scalp	5	1.3 (0.5,3.0)	14	3.5 (2.1,5.8)	2.2 (−0.5,6.1)
	Rashes elsewhere on body	137	35.7 (30.9,40.5)	136	34.3 (29.7,39.2)	−1.3 (−8.6,5.6)
Behavioral	Change in eating behavior	122	31.8 (27.1,36.6)	136	34.3 (29.7,39.2)	2.6 (−4.3,9.9)
	Change in sleeping behavior	101	26.3 (22.0,30.9)	90	22.7 (18.7,27.0)	−3.6 (−10.6,2.8)
	Hyperactivity or synonym	23	6.0 (4.0,8.7)	15	3.8 (2.1,6.0)	−2.2 (−7.0,1.5)
	Irritability or synonym	96	25.0 (20.8,29.6)	114	28.8 (24.4,33.3)	3.8 (−2.8,10.9)
Poisoning	Lead	4	1.0 (0.4,2.6)	5	1.3 (0.5,2.9)	0.2 (−2.1,3.8)
Trauma	All	38	9.9 (7.2,13.3)	59	14.9 (11.7,18.7)	5.0 (−0.1,11.0)
Lymphadenopathy	All	26	6.8 (4.6,9.6)	19	4.8 (2.9,7.3)	−2.0 (−7.0,2.0)
Viral or infectious	Viral infection†	15	3.9 (2.2,6.2)	17	4.3 (2.5,6.7)	0.4 (−3.1,4.9)
Urological	Enuresis	5	1.3 (0.5,3.0)	9	2.3 (1.1,4.1)	1.0 (−1.6,4.7)
Cardiac	Heart murmur	7	1.8 (0.9,3.6)	9	2.3 (1.1,4.1)	0.4 (−2.3,4.4)

* Signs and symptoms found in $> 1\%$ of children and which had a difference of > 1 reported between treatment groups.

† Viral infection other than upper respiratory infection.

Table 3. *Children with abnormal laboratory values at clinical centers' local laboratories by treatment group*

Laboratory test	Criteria	Placebo (n = 374) No.	Placebo (n = 374) Proportion (95% CI)	Succimer (n = 383) No.	Succimer (n = 383) Proportion (95% CI)	Difference in proportion (succimer − placebo) Difference (95% CI)
Heme/lymphatic						
Platelet count	<150,000/mm^3	12	3.2 (1.8, 5.5)	19	5.0 (3.0,7.6)	1.8 (−1.7,6.4)
	Confirmed	1	0.3 (0.0, 1.4)	0	0.0 (0.0,0.9)	−0.3 (−2.6,1.4)
Absolute neutrophil count	<800/mm^3	36	9.6 (6.8, 13.0)	43	11.2 (8.2,14.8)	1.6 (−3.3,7.4)
	Confirmed	5	1.3 (0.5, 3.1)	3	0.8 (0.2,2.2)	−0.6 (−4.0,1.8)
Metabolic						
Alkaline phosphatase	>local upper limit of normal*	146	39.0 (34.2, 44.0)	148	38.6 (33.7,43.7)	−0.4 (−7.9,6.7)
	>5× local upper limit of normal	7	1.9 (0.9, 3.7)	9	2.4 (1.2,4.3)	0.5 (−2.3,4.5)
	Confirmed > 5× local upper limit of normal	2	0.5 (0.1, 1.9)	2	0.5 (0.1,1.8)	0.0 (−3.2,2.1)
Aspartate aminotransferase	> local upper limit of normal†	157	42.0 (36.9, 46.9)	163	42.6 (37.6,47.6)	0.6 (−6.6,8.0)
	> 2× local upper limit of normal	12	3.2 (1.8, 5.5)	9	2.4 (1.2,4.3)	−0.9 (−5.1,2.3)
	Confirmed > 2× local upper limit of normal	0	0.0 (0.0, 0.9)	1	0.3 (0.0,1.4)	0.3 (−1.3,2.6)
Alanine aminotransferase	> local upper limit of normal‡	15	4.0 (2.3, 6.4)	27	7.0 (4.7,10.1)	3.0 (−0.8,8.0)
	> 2× local upper limit of normal	4	1.1 (0.4, 2.7)	3	0.8 (0.2,2.2)	−0.3 (−3.7,2.0)
	Confirmed > 2× local upper limit of normal	0	0.0 (0.0, 0.9)	1	0.3 (0.0,1.4)	0.3 (−1.3,2.6)

* Alkaline phosphate local upper limit of normal (U/L): Baltimore, 320 (Hopkins/U Maryland), 490 (University Hospital); Newark, 270 (0–2 y) and 415 (>2 y); Philadelphia, 131; Ohio, 400 (Columbus), 305 (♂) and 390 (♀) (Cincinnati).

† Aspartate aminotransferase local upper limit of normal (U/L): Baltimore, 35 (Hopkins/U Maryland), 40 (University Hospital); Newark, 42 (0–2 y) and 65 (>2 y); Philadelphia, 30; Ohio, 75 (Columbus), 35 (Cincinnati).

‡ Alanine aminotransferase local upper limit of normal (U/L): Baltimore, 30 (Hopkins/U Maryland), 45 (University Hospital); Newark, 60 (0–2 y) and 50 (>2 y); Philadelphia, 35; Ohio, 150 (Columbus), 30 (Cincinnati).

is a decrease of approximately 2–3 points (17). The blood lead levels in TLC started out higher than that, but the difference in blood lead levels between the children given succimer and those given placebo exceeded 10μg/dL only briefly, and averaged 4.7 μg/dL (0.2 μM) during the 6 mo after treatment was begun. In addition, in a short-term study using lead-exposed adult rhesus monkeys, succimer did not lower brain lead levels whereas cessation of exposure did (18). However, succimer is as effective a chelating agent as is available, and we used a very aggressive dosing regimen and had high rates of adherence and retention. The 6 m to 1 y that the blood lead levels were lower is approximately one-third of the children's lives. It is unlikely that another chelation regimen would be more effective in these children. We are following the children through age 7 y with tests of cognitive, behavioral, and neuropsychological function, and will be able to speak to the efficacy of succimer in preventing lead-associated impairment when those data become available.

Succimer at these doses in healthy children lowers lead levels with little or no obvious toxicity. Caution is warranted by the finding of excess hospitalization for trauma as well as more frequent signs of trauma in the children taking succimer, but this could be because of chance and was not an *a prior* hypothesis.

Acknowledgments. The authors thank T. Shaffer, Program Support Center, U.S. Department of Health and Human Services, Perry Point, MD, U.S.A., and E. Helzner, McNeil Consumer Products, Fort Washington, PA, U.S.A. Chemet and placebo were gifts from McNeil.

REFERENCES

1. Pirkle JL, Kaufmann RB, Brody DJ, Hickman T, Gunter EW, Paschal DC 1998 Exposure of the U.S. population to lead, 1991–1994. Environ Health Perspect 106:745–750
2. Dietrich KN, Succop PA, Berger OG, Hammond PB, Bornschein RL 1991 Lead exposure and the cognitive development of urban preschool children: the Cincinnati lead study cohort at age 4 years. Neurotoxicol Teratol 13:203–211
3. McMichael AJ, Baghurst PA, Wigg NR, Vimpani GV, Robertson EF, Roberts RJ 1988 Port Pirie cohort study: environmental exposure to lead and children's abilities at the age of four years. N Engl J Med 319:468–475
4. Bellinger D, Sloman J, Leviton A, Rabinowitz M, Needleman HL, Waternaux C 1991 Low-level lead exposure and children's cognitive function in the preschool years. Pediatrics 87:219–227
5. Dietrich KN, Berger OG, Succop PA, Hammond PB, Bornschein RL 1993 The developmental consequences of low to moderate prenatal and postnatal lead exposure: intellectual attainment in the Cincinnati lead study cohort following school entry. Neurotoxicol Teratol 15:37–44
6. Bellinger DC, Stiles KM, Needleman HL 1992 Low-level lead exposure, intelligence and academic achievement: a long-term follow-up study. Pediatrics 90:855–861
7. Nightingale SL 1991 Succimer (DMSA) approved for severe lead poisoning. JAMA 265:1802–1802
8. Graziano JH, Lolacono NJ, Meyer P 1988 Dose-response study of oral 2,3-dimercaptosuccinic acid in children with elevated blood lead concentrations. J Pediatr 113:751–757

9. Centers for Disease Control and Prevention 1991 Preventing lead poisoning in young children. U.S. Department of Health and Human Services, Centers for Disease Control, Atlanta, GA
10. Treatment of Lead-exposed Children Trial Group 1998 The Treatment of Lead-exposed Children (TLC) Trial: design and recruitment for a study of the effect of oral chelation on growth and development in toddlers. Paediatr Perinat Epidemiol 12:313–333
11. Rogan WJ, Ragan NB, Damokosh AI, Davoli C, Shaffer TR, Jones RL, Wilkens S, Heenehan MC, Ware JH, Henretig FM 1999 Recall of a lead-contaminated vitamin and mineral supplement in a clinical trial. Pharmacoepidemiol Drug Safety 8:343–350
12. Rhoads GG, Rogan WJ 1996 Treatment of lead-exposed children. Pediatrics 98:162–163
13. Cleveland WS, Devlin SJ 1988 Locally weighted regression: an approach to regression analysis by local fitting. J Am Stat Assoc 83:596–610
14. Cleveland WS 1993 Visualizing data. Hobart Press, Summit, NJ, pp 88–104
15. Chambers JM, Hastie TJ 1993 Statistical models in S. 2nd ed. Chapman and Hall, New York, pp 309–373
16. O'Connor ME, Rich D 1999 Children with moderately elevated lead levels: is chelation with DMSA helpful? Clin Pediatr Phil 38:325–331
17. Pocock SJ, Smith M, Baghurst P 1994 Environmental lead and children's intelligence: a systematic review of the epidemiological evidence. BMJ 309:1189–1197
18. Cremin JJ, Luck M, Laughlin N, Smith DR 1999 Efficacy of succimer chelation for reducing brain lead in a primate model of human lead exposure. Toxicol Appl Pharmacol 161:283–293

APPENDIX

TLC Steering* and Publication Committee: R.L. Bornschein*, J.J. Chisolm, Jr.*, A.I. Damokosh, D.W. Dockery, M.E. Fay, R.L. Jones*, G.G. Rhoads* (Steering Committee Chair), N.B. Ragan, W.J. Rogan*, M. Salganik, D.F. Schwarz*, J.H. Ware*, and R.P. Wedeen*.

TLC Investigators—TLC Clinical Centers: Baltimore, MD, U.S.A.: J. Serwint, Johns Hopkins Hospital; M. Brophy, J.J. Chisolm, Jr., C.T. Davoli, M.B. Denckla, M.R. Farfel, and G.W. Goldstein, Kennedy Krieger Institute; J. Rubin, University of Maryland; Cincinnati/Columbus, OH, U.S.A.: O. Berger, R.L. Bornschein, K.N. Dietrich, C. Wesolowski, and S. Wilkins, University of Cincinnati Medical Center; G. Maynard-Wentzel, and M.E. Mortensen (to 1994), Children's Hospital of Columbus; Newark, NJ, U.S.A.: S. Adubato, M. Elsafty, M. Heenehan, A. Sheffet, A. Ty (to 1997), and R.P. Wedeen, University of Medicine and Dentistry of New Jersey/New Jersey Medical School; G.G. Rhoads, University of Medicine and Dentistry of New Jersey/Robert Wood Johnson Medical School; Philadelphia, PA, U.S.A.: C. Campbell, F.M. Gill (to 1996), J. Guinn, F. Henretig, D. Knight, J. Radcliffe, and D.F. Schwarz, The Joseph Stokes, Jr Research Institute, Children's Hospital of Philadelphia; Central Laboratory: B.B. Bowman (to 1996), E. Gunter, D. Huff, R.L. Jones, D.T. Miller (to 1995), and D.C. Paschal, Nutritional Biochemistry Branch, CDC; Data Coordinating Center: A.J. Bernstein, A.I. Damokosh, D.W. Dockery, M.E. Fay, T.V. Kotlov, M. Salganik, and J.H. Ware, Harvard School of Public Health; National Institute of Environmental Health Sciences Project Office: N.B. Ragan, and W.J. Rogan; Data and Safety Monitoring Committee: C.R. Angle, J. Faison, S.H. Gehlbach (Chair), B. Gray-Little, S.A. James, L.A. Moyé, and H.L. Needleman.