# The Impact of Succimer Chelation on Blood Cadmium in Children with Background Exposures: A Randomized Trial

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Succimer lowers blood lead concentrations in children, and the structure of succimer chelates of lead and cadmium are similar. Using blood samples from a randomized trial of succimer for lead poisoning, however, we found that succimer did not lower blood cadmium in children with background exposure. *(J Pediatr 2013;163:598-600).*

Cadmium is well-established as a toxic metal; the best studied detrimental effects include renal toxicity, hypertension, and skeletal disorders.[1] Exposure routes in children include diet, environmental tobacco smoke, and house dust.[2] Although the results from studies of morbidity are inconsistent, some have reported neurodevelopmental toxicity of background exposure to cadmium in children,[3,4] with the most recent showing that early-life background cadmium exposure was associated with lower IQ.[5] There is also a potential for acute poisoning, most recently from toys which, once lead was restricted, were reformulated with cadmium.[6] No drug is known to reduce body stores of cadmium in children.[7] We carried out a clinical trial of succimer for treating pediatric lead poisoning. Cadmium is sufficiently similar to lead in the in vitro structure of the chelated metal complexes to suggest comparable impact of chelation in vivo,[8] and we evaluated the effect of succimer for reducing cadmium at little additional cost and with no further risk to human subjects.

## Methods

The blood samples and data in this study come from the Treatment of Lead-exposed Children trial, a 4-site, placebo-controlled randomized study. The study was approved by the Institutional Review Boards at the clinical sites, the Centers for Disease Control and Prevention, and the National Institute of Environmental Health Sciences. We randomized 780 children, 396 to succimer and 384 to placebo. Details of the study were described previously.[9] The Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention analyzed all blood samples drawn before randomization (baseline) and 1 week after treatment began (1-week), at which the lowest blood lead was produced by succimer.[10] Whole blood specimens were analyzed using inductively coupled plasma mass spectrometry.[11] The limit of detection (LOD) of blood cadmium was 0.2 $\mu$g/L.

| | |
|---|---|
| LOD | Limit of detection |

We estimated the median, 75th percentile, and 90th percentile and corresponding 95% CI of blood cadmium. For concentrations below the LOD, we substituted for LOD divided by the square root of 2, although imputing any other value between zero and LOD would have no impact on inference about the selected percentiles. The difference between blood cadmium at baseline and after treatment within each treatment group was examined by the Skillings-Mack test.[12]

To evaluate the impact of succimer on blood cadmium concentration, the difference between the selected percentile of blood cadmium in the placebo group and the succimer group was tested using a linear quantile regression model, adjusted for baseline blood cadmium, age, sex, race, center, and body surface area (the basis to calculate the dose). Because socioeconomic factors may affect compliance of participants, which would in turn affect the results of clinical trials,[13] we also adjusted for available socioeconomic factors (ethnic group, language, parent's education, annual family income, parent's working status, and whether living with single parent). Although blood cadmium is not normally distributed, there was no need to transform it because of the invariant property of estimators under positive monotone transformations in quantile regression.[14] The intention-to-treat assignment was used in the analyses.

## Results

The two treatment groups were balanced with respect to baseline characteristics.[15] The proportions of censored data are 43% and 45% for baseline and 1 week, respectively, which

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**Table I.** Median, 75th, and 90th percentile of blood cadmium concentrations (μg/L) by time point and treatment group

| | Selected percentiles (95% CI) | | | |
|---|---|---|---|---|
| | 50th | 75th | 90th | Sample size |
| Placebo | | | | |
| Baseline | 0.22 (0.20, 0.23) | 0.28 (0.26, 0.29) | 0.34 (0.33, 0.39) | 374 |
| 1-week† | 0.22 (0.20, 0.22) | 0.27 (0.25, 0.28) | 0.32 (0.31, 0.36) | 379 |
| Succimer | | | | |
| Baseline | 0.21 (0.20, 0.22)* | 0.28 (0.27, 0.31)* | 0.37 (0.34, 0.42)* | 393 |
| 1-week† | 0.21 (0.20, 0.22) | 0.27 (0.26, 0.30) | 0.38 (0.34, 0.41) | 389 |

*No difference with placebo group determined by quantile regression model ($P > .05$), after adjusting for age, sex, race, center, body surface area, and socioeconomic factors.
†No difference with baseline determined by Skillings-Mack test ($P > .05$).

did not affect the estimates of percentiles above the median. The selected percentiles of blood cadmium concentration are shown in Table I. There was no difference in adjusted baseline blood cadmium concentrations between the placebo and succimer groups (Table I). Their blood cadmium concentration did not change between baseline and 1 week.

The between-group difference of effect of succimer was indicated by the coefficient for treatment in the linear quantile regression models of blood cadmium concentration on treatment and other covariates (Table II). For all subjects, except for the significant unadjusted coefficient in the 90th percentile regression model, both the adjusted and the unadjusted coefficients in the median, 75th, and 90th percentile regression models were close to 0 and not statistically significant.

## Discussion

Treatment of acute and chronic cadmium poisoning has been a topic of toxicologic and clinical interest for decades. In 1984, the journal *Environmental Health Perspectives* had a special issue on cadmium with an emphasis on chelation. The conclusion was that none of the agents then available had been shown to chelate cadmium safely[16]; in a 2005 review, Blanusa et al[7] noted that there was still no approved drug. Succimer was approved for pediatric lead poisoning in 1991, but has not been evaluated for effect in reducing blood cadmium. Succimer given orally promptly after oral cadmium in animals may diminish gastrointestinal absorption and cadmium retention in the tissues, but evidence for therapeutic efficacy after chronic cadmium exposure is lacking.[17-19] In our trial, we find that succimer has no effect on background blood cadmium concentrations resulting from background exposures in US children. Among children with the highest blood cadmium concentration, the blood cadmium was slightly increased after treatment (the unadjusted 90th percentile increased 0.06 μg/L with statistical significance) but the difference disappeared after adjustment. One reason that succimer may not reduce cadmium is that succimer is mainly distributed in the extracellular space, and cadmium is mostly bound intracellularly to metallothionein.[20,21] Another is that the cadmium concentrations here are low, and the analytic methods may not be precise enough to detect the small changes. (The power to find a 10% decrement in blood cadmium is less than 0.60.) In industrial settings, the trigger concentration of blood cadmium for medical action is 5 μg/L.[22]

We used all the data including non-detects (accounting for 43% and 45% of the measured baseline and 1-week samples, respectively) in our analysis, but report results for percentiles above the median. Our results for the 75th and 90th percentile regression models are approximate to the coefficients of the median and 75th regression models if we excluded all the subjects with non-detects in our data.

Our results come from a large multicenter, placebo-control randomized trial of succimer and show that succimer has no effect on blood cadmium after 1 week, the point at which succimer shows maximum efficacy of 43% for reducing blood lead. The results from this study done on samples from a study designed for treating lead

**Table II.** Difference between groups in the median, 75th, and 90th percentile of blood cadmium concentrations (μg/L) after treatment

| | Median | | 75th percentile | | 90th percentile | |
|---|---|---|---|---|---|---|
| | Difference (95% CI) | *P* value | Difference (95% CI) | *P* value | Difference (95% CI) | *P* value |
| Unadjusted | −0.01 (−0.03, 0.01) | .22 | 0.00 (−0.03, 0.03) | 1.00 | 0.06 (0.02, 0.10) | <.01 |
| Adjusted* | 0.00 (−0.01, 0.01) | .98 | 0.00 (−0.01, 0.01) | .69 | 0.01 (−0.01, 0.02) | .42 |

*Adjusted for baseline blood cadmium, age, sex, center, body surface area, and socioeconomic factors.

poisoning may not be directly extrapolated to children with acute or high cadmium exposure. ■

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