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METALS

Lead Poisoning Treatment—A Continuing Need (Commentary)

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While pediatricians and toxicologists can't help but be pleased by the recent dramatic reductions in the number of children with lead poisoning, there remain in this country an estimated 890,000 children with lead levels of 10 μg/dL (the current level of concern) or greater. Of these there are approximately 275,000 children with lead levels ≥ 15 μg/dL and 84,500 with lead levels ≥ 20 μg/dL (1). Particularly worrisome are recent data suggesting that detrimental effects of lead on neurodevelopment can be demonstrated in children with lead levels as low as 5 μg/dL (2), magnifying the scope of this potentially devastating, completely preventable environmental illness of childhood.

For those of us who have invested time and career to the management of childhood lead poisoning, it has never felt comfortable to say to parents of children with lead levels greater than 20 μg/dL that there was no treatment to offer. Therefore a common (but far from unanimous) approach has been one of aggressive management, including chelation therapy in selected cases. And, while many organizations, including the American Academy of Pediatrics, have suggested that there is no clear reason to chelate children with lead levels below 45 μg/dL (3), other organizations, including the Centers for Disease Control, have stated that there is potential value to chelation in selected cases and that it should at least be considered in children with lead levels of 20–25 μg/dL (4).

Chelation for ''moderate childhood lead poisoning'' (20–44 μg/dL) has been proven to have some value, demonstrated by the normalization of δ-aminolevulinic acid dehydratase and Vitamin D activity or in erythrocyte protoporphyrin concentrations in blood (5–7). However, the outcome measure of greatest interest has been the effects of chelation therapy on childhood neurodevelopment. This question is certainly appropriate when one considers that the detrimental effects of lead on a child's brain are thought to be permanent and have lifelong implications. There has been a hope, buttressed by imperfect studies, that chelation therapy in lead-poisoned children could either reverse the neurodevelopmental injury caused by lead poisoning or, at least to arrest the process of ongoing central nervous system injury. The recognition that the first 3 years of life were the most vulnerable periods for lead's neurotoxic effects provided further reason to optimistically chelate young children with moderate lead burdens.

Against this background, recently published results of the TLC trial (Treatment of Lead Poisoning in Children) by Rogan and colleagues was an unprecedented research accomplishment (8). The authors are to be congratulated for producing such a rigorous study. Solely investigating the efficacy of succimer in improving neurodevelopmental outcome in a cohort of lead poisoned children, the study was a placebo-controlled clinical trial with 3-year follow. Unfortunately, the findings were unwelcome—succimer chelation had no apparent value in improving neurodevelopmental score. Based on the findings of the study, the authors state that there are no

data to justify the chelation of any child with a lead level below 45 μg/dL.

Despite the study's rigor, it is important to closely analyze its methodology to identify major shortcomings before its findings lead us to make unjustifiable conclusions on how best to care for moderately lead poisoned children.

This study has several significant flaws. First, the authors, by their own admission, were unable to produce enduring reductions in blood lead level with succimer. After 6 months, receiving as many as 3 courses, treated children had mean blood lead levels that were a mere 4.5 μg/dL lower than those in the untreated group; at one year, intergroup differences had disappeared. Moreover, there was no evidence, e.g., a documented fall in erythrocyte protoporphyrin activity, that succimer was reducing the concentration of lead in soft tissues, e.g., bone marrow (and presumably brain).

The mean lead level of the study population was 26 μg/dL yet the investigation purports to examine the effects of succimer on children with blood lead levels of 20–44 μg/dL. A subgroup or stratified analysis would have been extremely valuable in determining if the effects of succimer were uniform across all lead levels in this broad range.

It is striking that in this cohort of 780 children the mean maternal IQ was 80. This unusual finding may simply reflect the fact that lead poisoning occurs predominantly among a select population of poor, economically-deprived families. Regardless of potential explanations, this population clearly is not representative of the US population or even among all lead-poisoned children. For example, in the Children's Hospital Boston Pediatric Environmental Health Center, an estimated 35–40% of lead-poisoned children have professional, middle- to upper middle-class parents. It is doubtful that these children would have the same results as those from the Rogan study.

The authors, in making the decision to test only one outcome measure of chelation miss an opportunity to examine nonneurodevelopmental benefits of chelation therapy. The efficacy of chelation in improving the function of several organs, e.g., hematopoietic tissues, are clear and reproducible. Leaving the final message that chelation is valueless in children with moderate lead poisoning ignores these proven benefits.

Finally, the authors conclude by stating ''there is no chelator better than succimer,'' extending their findings to all the agents used in the treatment of lead poisoning. Such a broad-sweeping statement ignores the evidence that agents including *d*-penicillamine, 2,3-dimercapto-1-propanesulfonate (DMPS), and 2,3-dimercapto-1-propanol (BAL) are efficacious in reducing lead burden. Of these, *d*-penicillamine has been the most extensively used. Studies from our center and by others have documented the efficacy (and potential adverse effects) of penicillamine (9–13). Admittedly the efficacy of these agents in improving neurodevelopmental outcome is unstudied.

Collectively these shortcomings should make pediatricians and toxicologists uneasy about the prospect of providing no chelation therapy to any child as long as their lead level is <45 μg/dL, particularly if the child also has an elevated erythrocyte protoporphyrin. A careful risk-benefit analysis should be performed with each case. What are the risks of chelation? What are its potential benefits, both developmental and nondevelopmental? The results of such an analysis will determine the comfort level that physician and parent should have about non-treatment.

This year our Center will treat more than 200 new children with moderate lead poisoning. The patients will be economically and ethically diverse. And, after lead-safe housing is provided and nutrition is optimized, the question of chelation will arise in those with persistently elevated lead levels. We will continue to offer chelation therapy to many of these families because, in following their erythrocyte protoporphyrin levels during chelation, we will be able to demonstrate our successful reduction in their lead burden. The Rogan study will undoubtedly give us pause and require that we be candid in informing families about the risks versus potential benefits of chelation therapy. But, in offering agents with minimal risks and potential benefits, we continue to believe that we are, in the long run, helping these children.

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