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METALS

Lead Poisoning Prevention, Not Chelation (Commentary)

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The Metals Issue offers the opportunity to put into writing some of the impromptu comments I made at the conclusion of Dr. Allister Vale's eloquent keynote lecture on chelation therapy for plumbism at the 21st European Association of Poison Centre's and Clinical Toxicologists meeting in Barcelona, Spain in May 2001. The report under discussion was ''The Effect of Chelation Therapy with Succimer on Neuropsychological Development in Children Exposed to Lead.'' Rogan, W.J.; Dietrich, K.N.; Ware, J.H.; Dockery, D.W.; Salganik, M.; Radcliffe, J.; Jones, R.L; Ragan, N.B.; Chisolm, J.J.; Rhoads, G.G. N. Engl. J. Med. **2001**, *344*(19), 1421–1426. In discussing the relative quality of the cited study, and its impact on current practice in the care of children with lead poisoning, I acknowledged then, and will repeat here, that I was a clinical investigator at the Children's Hospital of Philadelphia Center for the study, and so might be biased in favor of the study's merits.

The Treatment of Lead-Exposed Children (TLC) study was designed to test the hypothesis that succimer therapy would improve scores of neurocognitive development in young children with moderately elevated (20–44 μg/dL) blood lead levels (BLLs). As I imagine most readers of the Journal have seen the paper, or have access to it, I'll omit a detailed description of the study methods. In brief, 780 children were enrolled in a randomized, double-blind, placebo-controlled trial. Up to 3 courses of therapy with succimer were administered, based on follow-up lead levels of 15 μg/dL or higher 2 weeks after the end of each course of therapy. Enrolled patients were provided home lead remediation and vitamin-mineral supplementation. Children were followed closely with periodic BLLs, measures of growth, blood pressure, laboratory studies including blood counts and relevant serum chemistries, and with developmental assessments at baseline and over a 36-month follow-up period. The primary findings included a predictably more rapid drop in mean BLL in the succimer-treated group, with clearly lower BLLs over 6 months but a near disappearance of such difference after 12 months of follow-up. During treatment with succimer, 10 of 396 children developed BLLs in excess of 44 μg/dL, compared with 7 of 384 who were given placebo. At 36 months of follow-up, there were no significant differences in any of the measures of neurocognitive function. And, of note, there was a small, but statistically significant decrement in growth velocity (0.35 cm over 36 months) in the succimer-treated children. The study authors conclude that ''these results suggest that drug therapy should be used with caution'' (my take: is not indicated) for treatment of young children with this degree of plumbism.

As for any such study, there are numerous potential weaknesses that might confound the study results and conclusions. Were the 2 groups balanced in terms of base-line characteristics, and representative of most children who might really be considered for such treatment in general clinical practice? Was randomization accomplished? It's possible that compliance was poor in the treatment group, or that the chosen course of therapy was

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not aggressive enough. Perhaps the outcome measures were insufficient or inappropriate?

I'd suggest that while imperfect, this study goes a long way towards addressing all of the above concerns. The study was conducted at 4 clinical centers that represent typical US inner-city populations of children exposed to lead-contaminated environments. A relatively large number of children were enrolled, and excellent randomization appears to have been achieved (essentially identical mean age, weight, and initial BLL in both groups; nearly identical baseline neurodevelopmental scores of both children and caretakers). Compliance with therapy was 90% by parental report, and 76% based on pill count, both impressive for studies of chronic drug therapy in children. The placebo pills were manufactured to look and smell the same as the succimer, in order to optimize blinding, as well as the likelihood of similar compliance in both groups. This seems to have been achieved, since some interruption in drug administration was nearly as frequent in the placebo group (27%) as in the succimer group (30%). The succimer dosing was based on body surface area, versus the more typical mg/kg regimen. At a mean weight of 12.3 kg for the enrolled subjects, this would typically result in initial total daily doses that were 50% greater. The initial ''high dose'' treatment was continued for 7 days, as opposed to the more typical 5 days, and each course of treatment was 26 days, versus the more typical 19 days. Thus, in comparison to the usual standard of care at the time the study was designed, the treatment plan was considerably more aggressive. Finally, 3 different measures of neurocognitive outcome were utilized. The Bayley Scales of Infant Development and the Wechsler Preschool and Primary Scales of Intelligence were used to approximate IQ. Second, a Developmental Neuropsychological Assessment, composed of a battery of tests to identify neurocognitive deficits that interfere with learning, was administered to look at domains of attentional, sensorimotor, visuospatial, language and memory function. Third, the Conners' Parent Rating Scale was used to determine parental assessments of their child's behavior in 3 particularly relevant areas: oppositional, hyperactivity and attention-deficit behaviors.

In my view, the TLC trial represents a hugely labor and time-intensive study that required the resources of the US National Institutes of Health to design, fund, and carry out. It's hard to imagine attempting a more comprehensive look at the impact of succimer therapy on the development of young children's minds, let alone one that could be reasonably applied to such a large group of randomized patients. The study will be continued for a large cohort of the initially enrolled patients, with further developmental testing when the children reach age 7 years. Until then, I think this is the best data we're likely to have, and it suggests rather strongly that, despite our best intentions to do something to help these kids, that drug therapy is not the answer. We need to redouble all our individual and societal efforts to prevent lead poisoning in the first place, and of course, to get diagnosed children into lead-safe housing. Most of us will continue to treat young, asymptomatic children with lead levels even slightly above 44 μg/dL with succimer, but in fairness, we ought to acknowledge to ourselves, and particularly to our patients' parents, that we really have little hard evidence to support that either! First, do no harm; second, be ever humble.

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