

CaEDTA Suppositories to Treat Elevated Blood Lead Levels in Children

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Summary: The test results clearly demonstrate the high level of effectiveness of removing lead from the human body with Calcium disodium EDTA rectal suppositories. The effect of lead poisoning on high percentages of the pediatric population is cause for concern. Lead poisoning is one of the most common and preventable pediatric health problems today. **Currently, the primary form of medical intervention consists of expensive and painful CaEDTA intramuscular injection.** The availability of an easily administered effective medical treatment is an important component in controlling the worldwide lead poisoning epidemic.

Introduction: Childhood lead poisoning is one of the most common pediatric health problems in the world today, and it is entirely preventable and reversible. Enough is now known about the sources and pathways of lead exposure, about ways of preventing this exposure, and about ways of reducing the lead content of the body to begin the efforts to eradicate this disease permanently. The persistence of lead poisoning, in light of all that is known, presents a singular and direct challenge to public health authorities, clinicians, regulatory agencies, and society.

Lead is ubiquitous in the human environment as a result of industrialization. It has no known physiologic value. Children are particularly susceptible to lead's toxic effects. Lead poisoning, for the most part, is silent: most poisoned children have no symptoms. The vast majority of cases, therefore, go undiagnosed and untreated. Lead poisoning is widespread. It is not solely a problem of inner city or minority children. No socioeconomic group, geographic area, or racial or ethnic population is spared.

Previous lead statements issued by the Center for Disease Control (CDC) have acknowledged the adverse effects of lead at lower and lower levels. In the most recent previous CDC lead statement, published in 1985, the threshold for action was set at a blood lead level of 25 mcg/dL, although it was acknowledged that adverse effects occur below that level. In the past several years, however, the scientific evidence showing that some adverse effects occur below levels at least as low as 10 mcg/dL in children has become so overwhelming and compelling that it must be a major force in determining how we approach childhood lead exposure.

It is not possible to select a single number to define lead poisoning. Epidemiological studies have identified harmful effects of lead in children at blood lead levels at least as low as 10 mcg/dL. Some studies have suggested harmful effects at even lower levels, but the body of information accumulated so far is not adequate for effects below about 10 mcg/dL to be evaluated definitively. As yet, no threshold has been identified for the harmful effects of lead.

Because 10 mcg/dL is the lower level of range at which effects are now identified, primary prevention activities are typically directed at reducing children's blood lead levels below 10 mcg/dL or 14 mcg/dL. While the overall goal should be to reduce children's blood lead levels below 10 mcg/dL, there are entrenched reasons for not attempting to do interventions directed at individual children to lower blood lead levels of 10-14 mcg/dL. First, practical medical interventions for children with blood lead levels in this range have previously been unavailable.

Second, the sheer numbers of children in this range would preclude effective case management in established intravenous therapy. Clearly, a simple and effective therapy such as suppository is needed.

The single, all-purpose definition of childhood lead poisoning has been replaced with a multi-tiered approach, described in the following table:

CLASS	Blood lead concentration (mcg/dL)	COMMENT
I	<10	A child in Class I is not considered to be lead poisoned.
IIA	10-14	Many children (or a large proportion of children) with blood lead levels in this range should trigger community wide childhood lead poisoning prevention activities. Children in this range may need to be rescreened more frequently. A decrease in blood lead level would be beneficial.
IIB	15-19	Child should receive nutritional and educational interventions and more frequent screening. If the blood lead level persists in this range, environmental investigation and intervention should be done. Non-invasive medical intervention should be done.
III	20-44	Environmental evaluation, remediation and a medical examination should take place. Such a child needs pharmacological treatment of lead poisoning.
IV	45-69	A child in Class IV will need both medical and environmental interventions, including even I.M. chelation therapy.
V	69>	A child with Class V lead poisoning is a medical emergency. Medical and environmental management must begin immediately.

Background: Lead is a poison that affects virtually every system in the body. The risks of lead exposure are not based on theoretical calculations. They are well known from studies of children themselves and are not extrapolated from data on laboratory animals or high-dose occupational exposure.

Since 1970, our understanding of childhood lead poisoning has changed substantially. As investigators have used more sensitive measures and better study designs, the generally recognized level for lead toxicity has progressively shifted downward. Before the mid-1960's, a level above 60 mcg/dL was considered toxic (Chisholm and Harrison, 1956). By 1978, the defined level of toxicity had declined 50% to 30 mcg/dL.

Lower blood lead levels cause adverse effects on the central nervous system, kidney and hematopoietic system. Blood lead levels as low as 10 mcg/dL, which do not cause distinctive symptoms, are associated with decreased intelligence and impaired neurobehavioral development (Davis and Svendsgaard, 1987; Mushak et al, 1989).

The concern about adverse effects on central nervous system functioning at blood lead levels as low as 10 mcg/dL is based on a large number of rigorous epidemiological and experimental studies. Several well-designed and carefully conducted cross-sectional and retrospective cohort studies in many different countries have been

conducted (Lansdown et al., 1986; Fulton et al., 1987; Fergusson et al., 1988; Silva et al., 1988; Bergomi et al., 1989; Hansen et al., 1989; Hatzakis et al., 1989; Winneke et al., 1990; Lyngbye et al., 1990; Needleman et al., 1990; Yule et al., 1981; Hawk et al., 1986; Schroeder et al., 1985) Some inconsistencies can be found in the results of these studies, but the weight of the evidence clearly supports the hypothesis that decrements in children's cognition are evident at blood lead levels well below 25 mcg/dL. No threshold for the lead-IQ relationship is discernable from these data. Recent evaluation of 24 major cross-sectional studies provides strong support for the hypothesis that children's IQ scores are inversely related to lead burden (Needleman and Gatsonis, 1990).

According to the Natural Resources Defense Council, blood lead levels as low as 10 mcg/dL, which do not cause distinctive symptoms, are associated with reading and learning disabilities, reduced attention span and behavioral problems.

The ramifications of the proliferation of lead pollution from industrialization combined with the devastating effects of health are sobering. A simple and effective therapy, such as EDTA chelation via suppository, is urgently needed.

Methods: A cluster of previously untreated children with high blood lead levels was desired for the purpose of testing the efficacy of Calcium disodium EDTA rectal suppositories to remove toxic metals from the human body.

1.) Determinization of study area: Friends of Lead Free Children, a non-profit organization connected to Columbia University and Fordham University, assisted in the search. A residential neighborhood in Haina, Dominican Republic as selected. The residential neighborhood was located adjacent to a battery recycling plant. All preliminary testing indicated 100% of residents as markedly toxic with lead.

2.) The selection of subjects into the study: Children who had been identified with blood lead levels over 10 mcg/dL were determined in a twenty four (24) hour urine collection by Ion Coupled Plasma Emission Spectroscopy. Hg. Analysis was determined by cold vapour mercury analysis.

3.) Individual treatment of lead overload: Cautious removal of lead from body depots was achieved through the use of Calcium disodium EDTA rectal suppositories. The use of suppositories provided for the prevention of local corrosive action of toxic metals on mucous membranes.

4.) Compensation: Compensation was not paid to subjects; however, no charges were incurred by participants for the drug and laboratory testing.

5.) Safety: By determining the concentration of heavy metals in the urine following provocative stimulation, the therapy with EDTA was scientifically determined, providing a safe treatment program. The study simultaneously provided diagnostic information regarding heavy metal burden as well as a defined treatment protocol for lead toxicity in a pediatric population. EDTA is a substance with low systemic and local toxicity and is generally well tolerated. The drug, per se, has been classified GRAS by the FDA, no cases of anaphylaxis have been reported through the oral administration of EDTA or through its use as a food additive.

6.) Alternative therapies: Alternative therapies were available for the treatment of metal intoxications, including (R,S)-2,3-dimercapto propane-1-sulfonic acid (DMPS) as well as its close standing analog DMSA. A significant advantage of using EDTA suppositories in a pediatric population include:

—a) Cooperative binding constant for lead.

—b) The suppository route of administration at bedtime was (is) an
— easy and acceptable delivery system.

—c) The antioxidant/free radical quenching role of EDTA made it
— superior over the other agents available due to the fact that

- neurological dysfunction was (is) recognized as a result of free
- radical mediated damage.
- d) EDTA was already approved for oral administration by the FDA
- and is on the GRAS list.
- e) EDTA is an ANTIDOTE to counteract the TOXIC action of
- lead from the environment.

7.) Medical care: Medical care was provided by Universidad de Autonomia de Santa Domingo. In the event of a medical emergency connected with the study, subjects were to contact the appropriate center, but this was never necessary. In addition, all participants could receive product and clinical information by calling: Ted Rozema, M.D., and principal investigator.

8.) Data coordination: Data was coordinated and maintained by the principal investigator, all data was statistically analyzed. Information was made available to all appropriate authorities, including IRB of the GLCCM and the FDA.

9.) Clinical laboratory: Clinical laboratory facilities and medical support was provided by AmScot Medical Laboratories, Inc. To ensure the safety and integrity of the study, the following analyses were assessed:

a) Baseline:

- Smac 18 with CBC - manual differential Blood lead determination
- Urine (24-hour collection) heavy metals to include: Pb, Cd, Hg, As, Ni, Al
- B2 - micro globulin (serum) Anti - TPO Total Ca/Ca²⁺ Mg/Mg²⁺ Pt/APTT PTH

— b) Provocative EDTA challenge:

- Blood lead determination
- Urine (9-hour) - heavy metals - Pb, Cd, Hg, As, Ni, Al
- B2 - micro globulin (serum) Total Ca/Ca²⁺ Mg/Mg²⁺ Pt/APTT PTH

—c) Mid-study laboratory evaluation:

- Blood lead determination
- CBC - manual differential Urine (9-hour) - heavy metals - Pb, Cd, Hg, As, Ni, Al
- B2 - micro globulin (serum)
- Total Ca/Ca²⁺ Mg/Mg²⁺
- Pt/APTT PTH

—d) Post study (6 weeks):

- Blood lead determination
- SMAC 18 with CBC - manual differential
- Urine (9-hour) - heavy metals - Pb, Cd, Hg, As, Ni, Al
- B2 - micro globulin (serum)
- Total Ca/Ca²⁺ Mg/Mg²⁺
- Anti-TPO
- PTH

Research Protocol: A study to determine the efficacy of Calcium disodium EDTA used as a rectal suppository in removing toxic metals from the human body. Subjects: children with proven lead toxicity (blood lead levels >10mcg/dL). Study design:

1.) Enrollment.

2.) Blood lead levels drawn to enter into study with simultaneous determination of urine lead excretion (total urine minerals - if possible with parental assistance).

3.) Treatment phase.

4.) Placement of a rectal suppository containing 2 grams of Calcium Disodium EDTA nightly for 10 days, then 10 days without EDTA, then placement of the EDTA suppository for 10 days, continue this program for two courses of treatment.

5.) Laboratory determinations:

	PRE	AFTER 10 DAYS	AFTER 10 DAYS	AFTER 10 DAYS
BLOOD	XX — Supp	XX — No supp	XX — Supp	XX
URINE	XX — Supp	XX — No supp	XX — Supp	XX

Purpose is to demonstrate gradual reduction of both blood and urine lead levels over time with a simple and cost-effective method.

It was anticipated that methods to reduce lead intake would be in place during and after this study. Unfortunately, no environmental mitigation was ever enacted.

Specimen Collection Regimen: Pre-study:

1.) Collection of 3 to 5 ml of whole blood in heparinized, lead-free cassettes.

2.) Collection of 9 hours of urine. This was measured from the time the child went to bed until 9 hours later. It was anticipated that the children were not getting up at night to urinate and mother would need to watch to catch the first morning specimen then determine when is the 9 hour point and collect the additional urine to make the complete collection

This provided a base line for both blood levels and excretion on a daily basis.

Just before the first suppository:

1.) Collection of 1 to 5 ml of whole blood in heparinized, lead-free cassettes.

2.) Insertion of the first suppository in the child's rectum, high as possible, just before the child goes to sleep, preferable with the child already in the bed.

The morning after the first suppository:

1.) Collection of 9 hours of urine. This was measured from the time the child went to bed until 9 hours later. It was anticipated that the children were not getting up at night to urinate and mother would need to watch to catch the first morning specimen then determine when is the 9 hour point and collect the additional urine to make the complete collection.

The morning before the 10th suppository:

1.) Collection of 3 to 5 ml of whole blood in heparinized, lead-free cures.

The morning after the 10th suppository:

1.) Collection of 9 hours of urine. This was measured from the time the child went to bed until 9 hours later. It was anticipated that the children were not getting up at night to urinate and mother would need to watch to catch the first morning specimen then determine when is the 9 hour point and collect the additional urine to make the complete collection.

The morning of the 19th day: This is the last day without a suppository before the next ten days of suppository administration.

1.) Collection of 3 to 5 ml of whole blood in heparinized, lead-free cures.

2.) Collection of 9 hours of urine. This was measured from the time the child went to bed until 9 hours later. It was anticipated that the children were not getting up at night to urinate and mother would need to watch to catch the first morning specimen then determine when is the 9 hour point and collect the additional urine to make the complete collection.

This gave us a determination of equilibration after no treatment for 10 days.

The morning of the 30th day:

1.) Collection of 3 to 5 ml of whole blood in heparinized, lead-free cures.

The morning after the 30th suppository:

1.) Collection of 9 hours of urine. This was measured from the time the child went to bed until 9 hours later. It was anticipated that the children were not getting up at night to urinate and mother would need to watch to catch the first morning specimen then determine when is the 9 hour point and collect the additional urine to make the complete collection.

All specimens were taken to the laboratory of Dr. Conrado Depratt at the Instituto De Quimica of the Universidad Autonoma de Santo Domingo.

Results: Average 20 children test data:

BLOOD LEAD LEVELS

Pre-study	66.64	mcd/gL
After 10 days of suppositories	39.09	mcd/gL
After 10 days without suppositories	61.45	mcd/gL
After 10 more days on suppositories	83.67	mcd/gL

URINE LEAD EXCRETION LEVELS

Pre-study	04.23	mcg/gL
After 1st suppository	325.55	mcg/gL
After 10 days of suppositories	61.445	mcg/gL
After 10 days without suppositories	9.04	mcg/gL
After 10 more days on suppositories	22.71	mcg/gL

The data clearly demonstrates that, (EDTA delivered in rectal suppository form), effectively removes lead from children with lead poisoning. The continued high excretion level, after 10 days without a Calcium disodium EDTA suppository is of special interest.

Also of special interest is the rebound effect in the blood lead levels. It's degree reflecting the high amount of stored lead in the tissue and bones and the attendant mobilization effect. Each time the blood lead level was diminished, additional lead was mobilized from the tissues and bones.

It was anticipated that methods to reduced lead intake would be in place during and after this study. Unfortunately, no environmental mitigation was ever enacted. Ideally, environmental intervention would have been enforced and the Calcium disodium EDTA rectal suppository therapy would have continued for a 6-month duration. This circumstance was not possible.