

EDTA Redistribution of Lead and Cadmium Into the Soft Tissues in a Human With a High Lead Burden – Should DMSA Always Be Used to Follow EDTA in Such Cases?

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Abstract

Intravenous sodium calcium ethylene diamine tetra acetic acid (EDTA) and oral 2,3-dimercaptosuccinic acid (DMSA) have both been used to reduce the burden of lead in humans. Each of these agents enhances the mobilization of lead from different areas of the body – EDTA from the trabecular bone and DMSA from the soft tissue. A study of Korean battery workers revealed that EDTA appeared to increase the soft tissue burden of lead, resulting in increased levels of aminolevulinic acid and greater subsequent lead mobilization with DMSA. This case report discusses a patient with a higher-than-normal lead burden who exhibited increased tissue lead burden after intravenous EDTA. The elevated tissue burden of lead was still present, albeit lower, after five consecutive days of oral DMSA therapy. If this single case is representative of a typical human response to the use of intravenous (IV) EDTA for lead, then it suggests that all persons undergoing such treatment should be administered oral DMSA for a minimum of one week after EDTA treatment.

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Introduction

Lead burden is a common finding in humans, with 90-95 percent of the total adult body burden of lead stored in the bones.¹ Blood lead is thought to reflect primarily current exposure, either from external or bioavailable internal sources. There is enough toxicokinetic difference among individual lead handling that the blood half life ($t_{1/2}$) is listed as “approximately 30 days.”² Although bone $t_{1/2}$ is 27 years,² that is also an approximation because bone lead is divided between relatively stable cortical bone (fairly inert lead pool) and trabecular bone (a more bioavailable lead storage site that is easier to chelate than cortical bone). Lead can also be found in the blood and in soft tissues.

Sodium calcium ethylene diamine tetra acetic acid (EDTA) has been the main therapeutic agent for lead poisoning for the last 50 years. It is generally administered intravenously (IV) because it is poorly absorbed from the gastrointestinal tract following an oral dose³ and because intravenous administration has been shown to accelerate lead excretion. Trabecular bone lead appears to be the prime target for IV EDTA.⁴ One concern with EDTA for lead chelation is the possibility that some of the lead will be redistributed from bone to soft tissue targets like the brain or kidneys.⁵

2,3-Dimercaptosuccinic acid (DMSA) is also a lead chelator and, like EDTA, has been used to treat lead intoxication. It is thought to be effective in removing lead from soft tissue and the blood, but to be ineffective for chelating bone lead.⁵ Redistribution of lead from bone to soft tissue targets is not thought to occur with DMSA.⁵

Changes in blood lead levels following EDTA are predictive of its efficacy. On the other hand, the lead removal efficacy of DMSA is better reflected by urinary aminolevulinic acid (ALA) levels.⁵ ALA is a substrate for the enzyme, delta-aminolevulinic acid dehydratase (ALAD), which catalyzes the second step in heme biosynthesis. ALAD is suppressed by the presence of lead, which, in turn, causes ALA to accumulate. Lee et al, working with individuals occupationally exposed to lead, found urinary ALA levels were predictive of DMSA-chelatable lead, while increases in blood lead were predictive of EDTA-chelatable lead. After EDTA administration, levels of ALA in the urine increased, indicating lead damage to heme biosynthesis. Higher levels of lead were flushed when DMSA was given two weeks after a challenge with EDTA compared to when

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DMSA was given before EDTA. Finally, they reported that lead excretion after DMSA was greatly increased if EDTA was given first.⁵ These findings suggest that EDTA might, in addition to causing lead to be excreted at an accelerated rate in urine, redistribute some lead from trabecular bone to soft tissues, and that DMSA might protect against and facilitate the removal of this redistributed lead. This redistribution is consistent with work by Cory-Slechta et al, who report that EDTA increases liver and brain lead levels in animals.⁴ In individuals with a high lead body burden, the potential redistribution by EDTA could have effects on more than heme synthesis; the concern is that some of these systemic effects could be serious. Because of the potential for lead redistribution to soft tissues, administering DMSA after each dose of EDTA might be warranted.

Blood lead remains the most recognized means of testing for current lead exposure, with blood lead levels reflecting current exogenous exposure and exposure from bioavailable body stores. Urinary lead is reflective of blood lead and may provide another means to estimate current exposure.^{6,7}

Case

A 55-year-old white male presented to the clinic with a chief complaint of amyotrophic lateral sclerosis (ALS). On his first visit, he was still able to walk with a cane. His history included making lead fishing weights as a youth. A six-hour, post-DMSA (2,250 mg oral DMSA in a single dose on an empty stomach with an empty bladder) urine sample was measured for heavy metal burden. Urine metals were analyzed by Inductively Coupled Plasma-Mass Spectrometry (ICP-MS) (Elan DRCII; Perkin Elmer Corp; Shelton, CT) at a commercial laboratory (Doctor's Data, Inc., St. Charles, IL). This initial urine test revealed post-challenge lead levels of 33 mcg/g creatinine (reference level: <5 mcg/g creatinine). The high lead level revealed on this oral DMSA challenge reflects high levels of bioavailable lead stored in soft tissues. Treatment with DMSA was begun using the following protocol: 750 mg DMSA three times daily for five days, followed by a rest of nine days. This DMSA treatment and recovery cycle was repeated four more times followed by a repeat urine test using the same challenge and collection protocol outlined above. The second DMSA challenge test resulted in a lead level of 27 mcg/g creatinine, which reflects a slightly lower tissue lead burden following the five cycles each of five days of oral DMSA.

Because of the still elevated post-DMSA challenge urine lead levels, it was decided that continued careful monitoring was required. On subsequent rechallenge with DMSA after the DMSA treatment cycles described above, the post-challenge urine test detected an exceptionally high lead level (9,100 mcg/g creatinine). Upon questioning it was revealed that the patient had recently begun taking five Ayurvedic products that were specially made for him by an Ayurvedic practitioner in India. These products were labeled as 1GB, 4P, 2ST, 3LT, and 5TIP and sent to Doctors Data for heavy metal testing. The results of the testing on these products are provided in Table 1. [Note: values listed in red under the 2ST column in Table 1 denote very high levels]

After receiving the test results, the patient agreed to stop using the products. Oral DMSA was continued for another 10 weeks before conducting the first of two EDTA-DMSA trials. The first EDTA-DMSA trial consisted of post-challenge urine testing only, while in the second trial both pre- and post-challenge tests were conducted.

The first trial spanned five days, with 2,000 mg IV EDTA administered on day 1 and 2,250 mg DMSA (body weight dose) given orally on days 2

Key words: EDTA, chelation, chelate, lead, cadmium, DMSA, heavy metal, ethylene diamine tetra acetic acid, dimercaptosuccinic acid, toxicity

Table 1. Results of Heavy Metal Testing of Five Ayurvedic Products

Metal (ppm)	1GB	4P	2ST	3LT	5TIP
Al	471	1,027	3731	60.3	96.1
As	7.28	0.829	99.9	1.53	<dl
Cd	0.487	0.442	5.94	0.079	0.076
Pb	8.71	7.54	56,185	10.49	1.12
Hg	21.9	4.66	6,333	6.81	0.574
Ni	2.79	5.45	11.8	0.269	1.68
Th	0.01	0.017	0.017	<dl	<dl
Sn	609	0.935	256.4	0.624	0.035

dl = detection limit

through 5. Results of urine testing, collected each day for six hours after chelation, are provided in Table 2.

Table 2. Urine Lead Levels in the First EDTA-DMSA Trial (urine in mcg/g creatinine)

	Post-EDTA	Post-DMSA	Post-DMSA	Post-DMSA	Post-DMSA
DAY	1	2	3	4	5
Pb	1,190	1,570	1,220	1,040	820

In the first EDTA-DMSA trial, urine lead levels were 1,190 mcg/g creatinine following day 1, when only IV EDTA was administered. Urine lead levels increased significantly following day 2 – when only oral DMSA was used – to 1,570 mcg/g creatinine. Urine lead levels declined progressively during the next three days of DMSA therapy. This first EDTA-DMSA trial demonstrated that the first day of DMSA resulted in greater urinary lead excretion than had occurred when EDTA had been administered. Since DMSA is believed to only chelate soft tissue and blood lead, this suggests that there might have been a significant amount of lead mobilized from bone with the EDTA that had not been excreted. The urine testing also suggests the continued treatment with DMSA caused a steady drop in the amount of soft-tissue lead; however, this first trial left several questions unanswered. As a result, a continuation of the study was requested, and both patient and lab agreed.

The second EDTA-DMSA trial involved a daily first morning (pre-challenge with EDTA or DMSA) and post-challenge urine collection. For six days, the patient collected first morning urine, followed by a six-hour collection after the chelating agent was administered. On the first day, with an empty bladder, he was given 2,000 mg IV EDTA with 10

mL of sterile water over 20 minutes prior to the six-hour urine collection. For the next five days, 2,250 mg DMSA was taken after voiding and on an empty stomach, followed by a six-hour urine collection.

The pre-challenge (first morning) urine was tested on day 1 and reflected circulating lead levels (blood level). The six-hour post-EDTA urine collection reflected chelatable lead burden (presumably lead mobilized from trabecular bone). The pre-DMSA urine tested on days 2-6, like pre-EDTA testing, reflected blood lead levels. The post-DMSA urine levels reflected an estimation of the chelatable blood and soft tissue lead.

On day 1, the first morning urine lead value was 2.3 mcg/g creatinine, which is either above (for years 2001-2002 and 2003-2004) or equal to (years 1999-2000) the 95th percentile published by the Centers for Disease Control (CDC).⁷ This level indicates current exposure, with the expectation of an elevated post-flush reading. Not surprisingly, the post-EDTA lead value was 160 mcg/g creatinine (a 69-fold increase), which is consistent with a significant mobilization of lead from trabecular bone. On the second morning, first morning urine lead levels were 31 mcg/g creatinine. This level was 13-fold higher than the first morning sample prior to EDTA provocation and indicates there was far more lead in the blood 24 hours after IV EDTA than there had been prior to treatment. It also suggests that further treatment to chelate the blood lead, as well as any lead redistributed to soft tissue, might be warranted. After the first day, DMSA was the chelating agent for the remainder of the trial. The first morning (pre-) and post-EDTA/DMSA lead levels for this second trial are listed in Table 3.

Urinary lead levels, a reflection of blood lead, increased significantly after EDTA administration and stayed elevated for the next five days, even with administration of 30 mg/kg DMSA daily. By the fifth day of DMSA therapy, the first morning urine lead value had decreased to 8.2 mcg/g creatinine, a level 3.5 times that of the pre-EDTA levels. DMSA treatment on the last day resulted in a substantial DMSA-induced increase in urine lead, suggesting there was still bioavailable lead to be chelated by DMSA. Because the elevated lead levels after five days of DMSA had not been anticipated, the trial was designed to last only six days. In an ideal

Table 3. First Morning (Pre-challenge) and Post-challenge Urine Lead Levels in the Second EDTA-DMSA Trial (mcg/g creatinine)

	Pre-EDTA	Post-EDTA	Pre-DMSA	Post-DMSA	Pre-DMSA	Post-DMSA	Pre-DMSA	Post-DMSA	Pre-DMSA	Post-DMSA	Pre-DMSA	Post-DMSA
DAY	1	1	2	2	3	3	4	4	5	5	6	6
Pb	2.3	160	31	61	17	78	15	57	16	91	8.2	45

situation, DMSA would have been continued until first morning lead levels were within a normal range.

Lee et al demonstrated that DMSA-chelatable lead is reflective of soft tissue levels.⁵ In this patient, the EDTA flush was not immediately preceded with a pre- and post-DMSA lead level. In retrospect, this would have been the best course of action (along with extending the number of days for post-EDTA DMSA chelation). A non-linear, up-and-down pattern for soft-tissue lead was observed in the post-DMSA lead levels between days 2 and 6. This pattern is quite different from the consistent downward trend observed during the first trial. While the values on day 2, 4, and 6 indicate a downward trend as seen in the previous test, the spikes on day 3 and 5 are contrary to this trend (particularly since the value on day 5 is the highest).

Cadmium Increase Similar to Lead

Because EDTA is considered to be an excellent chelator of cadmium, this metal was also monitored during the second EDTA-DMSA trial. Urine cadmium responses followed a similar pattern as lead in this patient (Table 4).

Urinary cadmium levels reflect both cumulative body burden and the level of cadmium in the kidneys.⁷ Since EDTA presumably reduced the body burden of cadmium, its elevation in the urine after the EDTA challenge likely indicates an increased kidney (soft tissue) burden. While DMSA is not as effective a mobilizer of cadmium as is EDTA, after five days of DMSA the first morning urine value for cadmium was almost back to baseline. These results suggest that EDTA might have redistributed some cadmium from bone to soft tissue and that DMSA helped reduce these levels.

Conclusion

The findings in this case report support the earlier work of Cory-Slechta and Lee that showed EDTA, while mobilizing lead from the bones, might increase both urinary and soft-tissue levels of lead and cadmium for a period of time after each EDTA treatment. DMSA appears to be effective post-EDTA in chelating this mobilized lead and accelerating its urinary excretion. Of importance is Lee's observation that large quantities of lead are excreted in the urine following EDTA, but that this is not the case with DMSA. This suggests that EDTA is more effective in mobilizing the body burden of lead than

Table 4. Urinary Cadmium Levels During Trial Two (mcg/g creatinine)

	Pre-EDTA	Post-EDTA	Pre-DMSA	Post-DMSA	Pre-DMSA	Post-DMSA	Pre-DMSA	Post-DMSA	Pre-DMSA	Post-DMSA	Pre-DMSA	Post-DMSA
DAY	1	1	2	2	3	3	4	4	5	5	6	6
Cd	1.1	5.3	3.2	2.3	2.4	3.0	1.7	1.7	1.4	1.9	1.5	1.4

DMSA. Lee also observed that DMSA-induced lead excretion was significantly greater if EDTA was given first, while giving DMSA prior to EDTA had no apparent effect on EDTA-induced lead excretion. This suggests a role for DMSA as a follow-up to EDTA for lead intoxication. Our findings in this patient support this potential role for DMSA as a post-EDTA therapy for lead intoxication. If this finding is reproduced in others with high lead burden, it may indicate that oral DMSA should be used after every IV-EDTA treatment for lead intoxication. This study also confirms that some Ayurvedic medications can contain exceptionally high heavy metal levels.

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