The Benefit of Pre- and Post-challenge Urine Heavy Metal Testing: Part 2

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Abstract

Measuring heavy metal levels in the urine is an accepted method for assessing the presence of a heavy metal burden in an individual. Random samples (without a flushing agent) are excellent for showing current exposures, as they reflect the level of heavy metals in the bloodstream during the hours immediately before bladder voiding. Samples taken after using a heavy metal mobilizing agent are a reflection of total body burden. Part 1 reviewed the benefits of doing pre-flush (baseline) testing utilizing the published Centers for Disease Control (CDC) heavy metal normal ranges for interpretation that allow the clinician to identify current exposures to lead and mercury and to identify cadmium toxicity. In part 2 the benefits of doing both pre- and post-challenge testing are reviewed. Information gleaned from performing both tests is unparalleled in allowing the clinician to identify which chelating agent will be most effective for the patient. If oral agents are employed, then possible absorption problems can be identified. Since none of these benefits are realized with only post-flush testing, it is recommended that clinicians do heavy metal testing both before and after a challenge with an effective and proven heavy metal mobilizing agent. The pitfalls of oral chelation in the case of malabsorption syndromes, such as gluten intolerance, are also discussed. *(Altern Med Rev* 2009;14(2):103-108)

Introduction

In part 1 of this article the benefits of doing a pre-flush, or baseline, measurement of urinary heavy metals were reviewed. New data published by the Centers for Disease Control (CDC) in their Third Report provide clinicians with national baseline reference values for urine heavy metals.[1] These numbers allow the clinician to identify current exposures by comparing patient results with national averages. Utilizing the CDC values for cadmium, along with information from studies published in Europe and Japan, also reveals cadmium toxicity with a baseline urine test. This is vitally important because cadmium toxicity has serious health implications and there are no published values that allow it to be identified after the use of a challenge agent – calcium ethylenediaminetetraacetic acid (Ca EDTA), dimercaptosuccinic acid (DMSA), or 2,3-dimercapto-1-propane sulfonic acid (DMPS).

When an unchallenged (pre-flush) test is followed by a challenge (post-flush) test using a chelating agent (DMSA, DMPS, Ca EDTA, or a combination), more pertinent information can be acquired than is available if only post-flush testing is done. This article focuses on the potential for this pair of tests to help the clinician identify the best heavy metal mobilizing agent for the patient, including the method of delivery – intravenous (IV) or oral. In order to best accomplish this task, the clinician needs to know the information in the pre-flush/baseline urine heavy metal test, as well as the heavy metal exposure history of the patient. By

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Table 1. The Differences in Arsenic, Cadmium, Lead, and Mercury Mobilization in One Adult with DMSA versus DMPS (µg heavy metal/g creatinine)

Metal	CDC 75%	Pre-flush (Baseline)	Post-DMSA	Post-DMPS
As	n/a	12.0	17.0	54.0
Cd	0.404	0.3	0.4	0.5
Pb	1.03		13.0	4.3
Hg	1.27	1.0	6.4	11.0

As=arsenic; Cd=cadmium; Pb=lead; Hg=mercury; n/a=not applicable

knowing the exposure history, it can be determined which heavy metals and at what levels they can be expected to be mobilized.

Exposure History

Finding significant heavy metal exposure in a client's history provides a reason to initially check for heavy metal burden. The obvious exposures to mercury disclosed during a patient history include the presence of occlusal amalgams (including how long they have been in the mouth) and both historical and current intake of high mercury fish[2] and high fructose corn syrup.[3] One should also check for a history of tobacco use, which contains the heavy metals arsenic and cadmium, including a history of exposure to secondhand smoke as a child. Knowing the hobbies and occupations of patients is also essential, as well as exposures of the mother prior to conception. Maternal transfer of heavy metals has been documented,[4,5] and is commonly seen in the author's clinical practice as well.[6] Other sources of heavy metal exposure include homes built before 1978 and the advent of lead-free paint and possible use of Ayurvedic or Chinese medicines.[7,8] The website www.scorecard.org can be helpful in finding unknown heavy metal exposures, as it allows the patient or clinician to determine whether high levels of heavy metals have been reportedly released by industry in a particular zip code.

When interpreting the post-flush urine test, one needs to keep in mind the exposure history (e.g., how much heavy metal is expected to be present), the amount of each heavy metal on the pre-flush/baseline test (if the pre-flush test shows current exposure then a much greater elevation of that compound on the post-flush test is expected), and what "normal" increases of the individual heavy metals should be expected with each individual mobilizing agent.

Expected Outcome: A Case Analysis

There is no single accepted protocol for flushed heavy metal testing with DMPS or DMSA. As a result, various amounts of these mobilizing agents are being used for differing amounts of time prior to urine collection, resulting in different levels of heavy metals being recovered on post-flush testing. A single protocol for the various agents that utilizes body-weight doses of DMSA (30 mg/kg oral), DMPS (3 mg/kg IV), and Ca EDTA (50 mg/kg IV) is followed in the author's office. Table 1 demonstrates the amount of arsenic, cadmium, lead, and mercury in the urine from a single individual when DMSA and DMPS were used separately.

Table 2. Pre- and Post-Flush Heavy Metal Levels (µg heavy metal/g creatinine)

Metal	CDC 75%	Pre-Metal Free	Post-Metal Free	Post-DMSA
Cd	0.404	0.3	0.3	0.7
Pb	1.03	<dl	<dl	28.0
Hg	1.27	1.9	0.7	33.0
Ni	n/a	1.5	1.1	2.1

dl=detectible levels; Ni=nickel

Observe that DMPS mobilized more arsenic and mercury than DMSA, while DMSA mobilized the most lead. These are both common findings based on the affinities of the chelating agents for the respective heavy metals and their potential to access heavy metal deposits. Neither agent mobilized very much cadmium even though both compounds have a high affinity for cadmium. This is because neither agent is able to enter the cells to chelate the cadmium, but can only bind to what is on the outside of cells.[9] An increase

Table 3. Heavy Metal Excretion (µg heavy metal/g creatinine): Comparison of DMSA, Oral Ca EDTA, and IV Ca EDTA

Metal	CDC 75%	Pre-DMSA	Post-DMSA	Pre-oral Ca EDTA	Post-oral Ca EDTA	Pre-IV Ca EDTA	Post-IV Ca EDTA
Cd	0.404	0.8	0.6	0.5	0.3	0.3	4.1
Pb	1.03	0.4	14.0	0.3	0.9	0.3	11.0
Hg	1.27	1.3	9.8	1.0	1.1	0.8	1.0
Ni	n/a	3.6	2.1	3.2	3.8	3.0	57.0

Table 4. Comparison of Zeolite with Ca EDTA/DMPS for Heavy Metal Chelation (µg heavy metal/g creatinine)

Metal	CDC 75%	Pre-Zeolite	Post-Zeolite	Post-Ca EDTA/DMPS
Cd	0.404	0.2	0.3	1.3
Pb	1.03	1.1	0.1	18.0
Hg	1.27	0.5	0.6	5.7
Ni	n/a	3.3	3.1	8.9

of 0.1-0.3 µg cadmium/g creatinine after DMSA is a common finding in the author's practice. This is one of the primary reasons a clinician needs to know the pre-flush or baseline cadmium levels in order to identify cadmium toxicity.

Lead levels increased from non-detectable to 13 after DMSA, while they increased to only 4.3 after DMPS – the opposite of mercury that went up 6.4-fold after DMSA and 11-fold after DMPS. This author typically observes that DMSA mobilizes twice as much lead and half as much mercury as DMPS. In order to yield the highest flush of lead, cadmium, and mercury, IVs of both Ca EDTA and DMPS can be used followed by a six-hour urine collection. This is reflective of the results observed by other clinicians the author has worked with.

Using pre- and post-flush heavy metal urine testing based on knowledge of exposure history to determine the most effective mobilizing agent is of importance for clinical efficacy as well as cost effectiveness. DMSA, DMPS, and Ca EDTA provide consistent results that are easy to interpret. Some other commonly available agents, however, may be more patient specific as the following examples demonstrate.

Comparison of Metal Free with DMSA

The following pre- and post-challenge tests were conducted on a 35-year-old female who had unsuccessfully attempted to conceive. Although the patient's amalgam fillings had been removed, she had several years of exposure to them. In addition, she ate fish regularly and had elevated blood mercury levels. She completed seven months of treatment with Metal Free, a commercially available product for mobilizing heavy metals (containing various ingredients including algae, probiotics, enzymes, ionic minerals, glycine, and glutathione). Table 2 compares pre-flush, post-Metal Free, and post-DMSA (following a two-week washout period) heavy metal levels.

Table 5. Heavy Metal Data (µg heavy metal/g creatinine) from a Patient Exposed to Multiple Mercury Amalgams

Metal	CDC 75%	Pre-DMSA	Post-DMSA
Pb	1.03	0.3	11.0
Hg	1.27	0.7	1.0

Table 6. Heavy Metal (µg heavy metal/g creatinine) Pre- and Post-DMSA Challenge Results in a Patient with Gluten Intolerance

Metal	CDC 75%	Pre-DMSA	Post-DMSA
Pb	1.03	<dl	6.6
Hg	1.27	0.8	4.5

As evidenced by the data in Table 2, the patient's baseline level of mercury is above the CDC's 75th percentile, indicating current exposure and verified by blood tests and a history of regular fish intake. With a pre-flush mercury level of 1.9 µg/g creatinine, one would expect a very elevated mercury level on the post-flush test, like the level of 33 µg/g creatinine that occurred with DMSA. Why then did the post-flush with Metal Free (which is said to clear metals via the urine) not only fail to enhance the mercury flush, but actually reduce by over 50 percent the amount of mercury loss that occurred without any assistance? The patient also had significantly elevated lead after the DMSA flush, although none was mobilized with the Metal Free, indicating DMSA would be the best agent for this person.

Oral Calcium EDTA

Numerous companies now sell oral capsules of Ca EDTA to enhance the mobilization of heavy metals. While this agent is clearly a powerful chelating agent when used intravenously, oral application has not been validated. Table 3 compares 3,000 mg oral Ca EDTA (pre and post) to oral body-weight doses of DMSA (30 mg/kg) and IV Ca EDTA (50 mg/kg up to 3,000 mg total).

This patient had exposure to cadmium and mercury just prior to the first pre- and post-DMSA flush testing. The subsequent tests (oral and IV Ca EDTA) were conducted 4-6 weeks apart. Pre-flush levels of cadmium began dropping without intervention, indicating the elevation initially was from a current exposure. Only IV Ca EDTA actually enhanced the excretion of this compound. The pre-flush levels of mercury also dropped over time, indicating current exposure just prior to the first test. Watching mercury reduction in the urine in light of the half-life of mercury in the blood (45 days for elemental and 70 days for methyl) is one method the clinician can use to determine amounts associated with current exposure and whether the patient is following avoidance recommendations. DMSA resulted in a 35-fold increase in lead output. Oral Ca EDTA resulted in a three-fold increase in lead excretion, while IV Ca EDTA enhanced the excretion 36-fold. DMSA provided a 7.5-fold increase in mercury, while both oral and IV EDTA yielded insignificant increases in mercury. DMSA was superior to either form of EDTA for chelation of mercury; IV EDTA and oral DMSA were both effective mobilizing agents for lead, while oral EDTA was not effective for this patient.

Oral Zeolite

Oral zeolite (an aluminosilicate adsorbent compound) is another commercially available agent for mobilizing heavy metals. Directions for doing a post-flush test with this agent, obtained from www.ncdtest.com, were followed with the exception that a pre-flush test was also conducted. Table 4 shows the results on a 32-year-old male of this agent on pre- and post-flush testing compared to post-flush testing with IV Ca EDTA and DMPS. A test prior to chelation with Ca EDTA or DMPS was not done because they were conducted within two weeks of each other.

This patient did not have an excessively high heavy metal burden, although he did have some bone lead, identified and effectively mobilized by IV Ca EDTA. His pre-flush test indicated a current lead exposure with a level of 1.1 µg/g creatinine. The zeolite not only failed to enhance the excretion of lead, it actually inhibited it by 91 percent, indicating it was an ineffective chelating agent for this particular patient.

Table 7. Heavy Metal Clearance (µg heavy metal/g creatinine) after Avoidance of Gluten Improves Absorption of DMSA

Metal	CDC 75%	Pre-DMSA with Positive Anti-gliadin Antibodies	Post-DMSA with Positive Anti-gliadin Antibodies	Post-DMSA after Gluten Avoidance
Pb	1.03	<dl	6.6	14.0
Hg	1.27	0.8	4.5	86.0

Table 8. Pre- and Post-DMSA Levels of Lead, Mercury, and Tin (µg heavy metal/g creatinine) in a Patient who Solders Stained Glass

Metal	CDC 75%	Pre-DMSA	Post-DMSA
Pb	1.03	0.5	2.0
Hg	1.27	0.8	3.7
Sn	n/a	1.2	13.0

Sn=tin

Using Pre- and Post-DMSA Testing to Identify Absorption Difficulties

When a pre-flush test is conducted to provide a baseline status and the clinician knows the patient's exposure history (and therefore the expected "dump"), a post-DMSA test can sometimes give excellent information about compromised absorptive ability of the small intestine. The author has even been able to identify several cases of gluten intolerance by utilizing this combination of tests. Table 5 is data from a patient who had multiple mercury amalgams, but no regular fish intake. The jump in mercury from 0.7 to 1.0 µg/g creatinine, only a 40-percent increase, is significantly lower than would be expected from a person with multiple amalgams. Typically, DMSA will yield at least a 10-fold increase in mercury elimination. Even though the lead posted a good increase in elimination, probably due to the greater affinity of DMSA for lead that allowed it to chelate soft-tissue stores, the small increase in mercury was troubling. A follow-up test for anti-gliadin antibodies showed positive anti-gliadin IgG antibodies, but negative anti-transglutaminase IgA antibodies. This means that this individual is eating gluten and reacting to it, but has not progressed to the state of celiac disease. However, the damage to the small intestinal villi from the positive anti-gliadin reaction seemed to reduce the ability of the small intestine to absorb DMSA.

In a second case, a 29-year-old female with six amalgams and a history of gluten intolerance reported she had removed all gluten from her diet. Her initial testing is outlined in Table 6. She had only about a five-fold increase in mercury elimination after a DMSA challenge, well below what is typically seen with this number of amalgams. Antibody testing revealed an elevated salivary anti-gliadin sIgA antibody level of 26 (normal 0-13; borderline 13-15; positive >15), but no anti-transglutaminase antibodies, indicating a gluten sensitivity and current dietary exposure. With sleuthing the source was finally identified in some discount-store supplements. Table 7 shows the difference in absorption capability resulting from six months of gluten avoidance after the supplements were discontinued.

A large difference in absorptive ability is observed after six months of gluten avoidance – from 4.5 µg mercury/g creatinine to 86 µg mercury/g creatinine – a 19-fold increase. Even with a negative anti-transglutaminase antibody test, indicating the absence of celiac disease, individuals with gluten intolerance may have malabsorption.

In a third case, a female, age 23, had seven amalgams since childhood and worked in her family business making stained glass pieces using solder that contained 40-percent lead and 60-percent tin. Her first pre- and post-DMSA test results are shown in Table 8. The DMSA challenge only resulted in a four-fold increase in lead and 4.6-fold increase in mercury, both well under what would be expected with her exposure history. Although there was a significant increase in tin,

Table 9. Oral versus IV Agents for Mobilizing Heavy Metals (µg heavy metal/g creatinine) in a Patient with Compromised Absorption

Metal	CDC 75%	Pre-DMSA (oral) with Positive Anti-gliadin Antibodies	Post-DMSA (oral) with Positive Anti-gliadin Antibodies	IV Ca EDTA/ DMPS
Pb	1.03	0.5	2.0	6.3
Hg	1.27	0.8	3.7	22.0
Sn	n/a	1.2	13.0	74.0

the low mercury and lead coupled with her exposure history pointed to possible malabsorption. Antibody testing yielded elevated anti-gliadin IgG antibodies at 11.6 (normal <10) and IgA antibodies of 7.4 (normal <5; Specialty Labs, Inc), although she was negative for anti-transglutaminase antibodies. Because of the elevated anti-gliadin antibodies, IV chelation was chosen, another method to determine whether a patient has malabsorption. Table 9 compares the results using oral versus IV mobilizing agents.

By bypassing the small intestine, intravenous chelation more accurately revealed this patient's true heavy metal burden. In all three cases, the use of pre- and post-testing, along with knowledge of the exposure history, also helped identify the presence of gluten intolerance, something that was unknown to two of the three patients. In the second case an unknown source of gluten was able to be identified. In all three cases, the patients were able to make life changes that should result in less morbidity associated with gluten intolerance. For an excellent review on the far-reaching effects of gluten intolerance the reader is directed to the review article in *Alternative Medicine Review* by Helms.[10]

Conclusion

By utilizing both pre- and post-challenge urine heavy metal testing, the clinician can gain valuable information that is simply not available from a single post-challenge test. When armed with the knowledge of the patient's exposure history, the clinician can identify the most efficient and cost-effective heavy metal mobilizing agent. The clinician is also able to identify whether the patient has previously undiagnosed malabsorption and may even be able to identify gluten sensitivity, something to consider when post-flush elimination is lower than expected from exposure history. Clinicians are strongly urged to perform a combination of pre- and post-flush testing in addition to obtaining a thorough history for heavy metal exposure.

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