Provocative Heavy Metal testing; which chelator is best?
By Marianne Marchese, ND

Physicians who practice environmental medicine often want to test patients for the presence of heavy metals in the body. Heavy metals such as mercury, lead, arsenic and cadmium have been linked to neurological, hormonal and immunological health problems. [1] Various methods exist for detecting heavy metals including hair analysis, serum tests, fecal and urine collection. It is important to understand the strengths and limitation of each method of testing in order to get accurate measurements.

Hair analysis can be used to test for recent exposure to heavy metals but it comes with many pitfalls. In 2001 a study was done where a split hair sample taken from the scalp of a single healthy volunteer was submitted for mineral analysis to 6 commercial US laboratories. Laboratory differences in the results exceeded 10-fold. Variations also were found in laboratory sample preparation methods and calibration standards. Laboratory normal reference ranges varied greatly, resulting in conflicting classifications (high, normal, or low) of nearly all analyzed minerals. [2] A review of the medical literature makes clear that physicians should not use hair analysis as the sole determinant of heavy metal toxicity due to unreliable results and poor reference ranges. [3] The Agency for Toxic Substances and Disease Registry, ATSDR, has made clear that many scientific issues need to be resolved before hair analysis can used in monitoring heavy metal exposure. [4]

Blood measurement of heavy metals can show what is present in the body at the time the blood is drawn. [5] Serum testing a good measurement of current exposure but not of what is stored in the body, referred to as body burden. Most commercial labs offering blood heavy metal testing have reference ranges set primarily for high dose, acute heavy metal poisoning. [6] The reference ranges are often set too high to detect low dose, chronic heavy metal exposure.

Urine heavy metal testing typically includes both a pre-challenge, also called un-provoked, and post-challenge or provoked urine collection. A pre-challenge test is a random urine collection and is a good measurement of chronic metal exposure. According to the ATSDR, “urine tests provide the best estimates of the current body burden of chronic mercury poisoning. Elemental and inorganic mercury are mainly excreted in the urine”. A pre-challenge urine test shows what metals are currently circulating in the body and being excreted by the kidney. It is important to make sure kidney function is intact prior to testing. If levels are high on an unprovoked test it means there is a current exposure to heavy metals. Some labs are using outdated reference ranges giving the appearance of a normal urine metal test. The Center for Disease Control has set new US references ranges for metals in the urine. These ranges are tighter than most commercial labs. http://www.cdc.gov/exposurereport

After completing an unprovoked or pre-challenge urine test to determine what the patient is currently being exposed to, a provoked or post-challenge urine heavy metal test should be run to determine past or chronic exposure to heavy metals. A provoked urine test involves giving a body weight dose of heavy metal chelator to the patient to pull metals from storage sites. Prior to administering this test the physician must run a complete blood count and comprehensive metabolic panel to ensure the liver and kidneys are functioning properly. After giving the dose of chelator the urine is collected for 6 hours and sent to the lab. A chelator binds minerals from the body as well as metals. Therefore it is necessary to replace minerals after a post-challenge test.

The downside to provocative heavy metal testing is that there are no set reference ranges. Labs that offer heavy metal testing set reference ranges for unprovoked urine testing and not

provoked. So if a patients test comes back with elevated levels of heavy metals I often ask, elevated in relation to what? Typically I will compare each patient's unprovoked urine test to their provoked urine test to determine if more heavy metals are in the body then what a random urine collection showed. Many physicians feel that a provoked urine test gives an estimate of body burden of metals. However, there is no way to know where the increase in heavy metal excretion is coming from on a provoked test. For example if lead shows up elevated on a provoked urine test is it merely circulating lead being pulled through the kidney, is it coming from the bone, extracellular spaces, or other sites. No matter where it is coming from it typically represent past or chronic exposure.

There are three proven chelators used for a provocative testing each giving very different test results. The key to getting an accurate measurement of heavy metals stored in the body is using the right chelator.

Several factors must be considered when deciding which chelator to use as a provoking agent. The first thing to consider is what metals has the patient been exposed to recently and over their lifetime. What are you testing for? What do you expect to find? To determine this, a comprehensive environmental history is taken to pinpoint what may be in the body. A history includes investigating possible exposures at home and at work, both past and present. Exposures related to hobbies, travel and lifestyle are investigated as well.

Second a thorough medical history and exam must be completed to correlate the patients' symptoms, disease, and illness to one or more metals. This involves knowing the toxicology of the most common metals and which conditions are linked to those metals. Heavy metals have been linked to chronic neurological and immune conditions as well as more subtle illness and symptoms. [7]

The last point to consider when determining which chelator to use for a post-challenge heavy metal test is an understanding of the key differences between the three most common chelators. Chelators form a complex with the heavy metal, binding the metal and excreting it in the urine. When performing provocative urine challenge test one of three chelating agents is used; calcium ethylenediaminetetraacetic acid (CaEDTA), dimercaptosuccinic acid (DMSA), or 2,3-dimercapto-1-propane sulfonic acid (DMPS).

DMPS is poorly absorbed when administered orally. Only 60% is bioavailable when administered by mouth. [8] This is why it is given as an intravenous push for heavy metal testing. Typical dose is 3 mg/kg slow push (10-15 minutes).

DMSA has been shown to be an effective chelator of lead and other heavy metals. It is absorbed well when given orally but can cause gastrointestinal upset. [9,10] The typical dose for provocative heavy metal testing is 30mg/kg by mouth. [9,10]

EDTA is approved by the Food and Drug Administration for lead poisoning and comes in two forms, calcium disodium ethylenediaminetetraacetic acid ($CaNa_2EDTA$), and calcium ethylenediaminetetraacetic acid (CaEDTA). $CaNa_2EDTA$ exchanges its calcium for lead and forms a complex for elimination from the body. Is has serious side effects including hypocalcaemia and several deaths have been reported with $CaNa_2EDTA$. [1] Therefore, CaEDTA is most commonly used for heavy metal testing and dosed 50mg/kg in a slow IV push, not to exceed 3g. [11]

DMPS does not redistribute lead, arsenic and organic mercury to the brain. [12]. DMSA decreases brain deposition of lead and methymercury. [12] Adverse reactions with DMSA or DMPS include elevated liver enzymes, gastrointestinal upset, skin reactions and neutropenia. [12] DMPS may cause hypotension if administered intravenously to rapid. [12] EDTA can cause

irritation at the site of injection, nephrotoxicity, skin reactions and myalgia. [13] CaEDTA does not cause hypocalcemia.

An ideal chelator has greater affinity for the metal to be bound, low toxicity, water solubility, and rapid elimination from the body. [1] When a chelator forms a complex with a heavy metal the chemical affinity of the chelator for the metal should be higher than the affinity of the metal for molecules in the body. Heavy metals have different chemical affinities. As a chelator binds metals with the highest affinity there is an increase in excretion of metals with lesser affinity. Each chelator pulls metals out in a different order. [14,15,16] When choosing a chelator for heavy metal provocative testing consider is best for binding different metals.

Metal	1st Choice	2nd Choice
Inorg. Mercury	DMPS	DMSA
Org. Mercury	DMSA/ DMPS	
Lead	DMSA/EDTA	DMPS
Arsenic	DMPS	DMSA
Cadmium	EDTA	DMPS*
Antimony	DMPS/DMSA	EDTA
Tin	DMPS,DMSA	EDTA
Thallium		DMSA

Heavy metal testing is an important part of an environmental medicine practice. Patients often suffer from health conditions linked to heavy metals in the environment. A prechallenge urine test followed by a post-challenge urine test gives the most accurate assessment of current and past heavy metal exposure. A thorough environmental exposure history, understanding what conditions are linked to heavy metals and knowledge of the three most common chelating agents can help the physician chose the most effective chelator when administering a heavy metal test.

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