# Metal Detoxification

## *General Information*

Chelating / metal binding agents bind to metal ions and mobilize them from tissue stores. A urinary metals challenge test (eg. provocation) is the best way to assess the net retention of metals. Most protocols require IV or oral administration of an agent followed by six hours of urine collection. During therapeutic metal detoxification, repeat provocative testing is highly recommended to monitor progress periodically throughout treatment. Commonly used and validated detoxification agents include EDTA, DMPS, and DMSA.

**Pre-provocative Testing**
Acute/ongoing metal exposure may also transiently increase urinary metal excretion. It is important to get a baseline unprovoked urine collection on the day of challenge to screen for acute exposures which may skew post-provocation results. This pre-provocation sample is often a first morning void, or a spot in-office collection prior to provocation.

**Creatinine Clearance Test**
Because administration of all of the agents can potentially cause a large efflux of metals to the kidneys, it is prudent to assess glomerular filtration prior to challenge. The creatinine clearance test is the gold standard for assessment, utilizing both serum and accurately timed urinary levels of creatinine. Especially in geriatric or low muscle-mass patients, serum levels of creatinine alone are not adequate for assessment of glomerular function.

**Adverse Reactions**
Severe reactions to the agents are relatively rare. Some patients experience mild upper-GI upset with oral agents, which is usually transient and can be alleviated by administering with a small amount of food. Patients with gastrointestinal dysbiosis may experience an exacerbation of symptoms with oral DMPS or DMSA, as the sulfhydryl agents appear to enhance proliferation of some bacteria and yeast. It is imperative to identify and treat dysbiosis **before** initiating an oral treatment protocol. A few small trial doses of oral DMPS or DMSA may be administered, at least 48 hours before the larger challenge dose to screen for potential severe adverse reactions.

**Patient Preparation**
Suspected sources of exposure should be avoided before provocation (eg., fish and shellfish should not be consumed for ~ 1 week prior to collection). Non-essential medications or dietary supplements should be discontinued for 48 hours prior to and during the specimen collection. Women should not collect while menstruating. The patient should be well hydrated **before** beginning the challenge. Only DDI containers may be used for specimen collection.

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**Comprehensive Laboratory Analysis**
Safe and effective treatment protocols for metal detoxification require support of the patient's kidney function, nutritional status, GI health / integrity, and identification and removal of sources of ongoing exposure. For a guide to comprehensive assessment, see the Toxic Metals: Comprehensive Laboratory Analysis flowchart.

**Interpretation of Results**
Reliable reference ranges have not yet been established for the provocative challenges. Provocation results are compared to reference ranges based on average urinary excretion in a healthy population under non-challenge/ unprovoked conditions. Affinities of the specific agents for the metals being tested (see chart below), dosage, and urine collection period must be considered in determining the significance of the results. Due to wide intraindividual variation in tolerance to toxic metals (associated with genetics, nutritional status, total toxic burden, exposure history, etc.); the patient's history and symptoms should also be considered to determine whether the levels of the excreted metals are likely causative or contributory factors in the patient's chronic illness (eg., if the patient should expect symptomatic improvement with detoxification therapy). The interpretive information supplied with the analysis identifies likely sources of exposure and symptoms of toxicity, which are also summarized in the Toxic Element Chart. Metal detoxification may also be undertaken for preventive measures, particularly in women of childbearing age who are not actively trying to conceive, and young children.

**Relative Affinities of Chelating Agent for Metals**

| Metal | 1st Choice | 2nd Choice |
|---|---|---|
| **Inorganic Hg** | DMPS | DMSA |
| **Organic Hg** | DMSA/ DMPS | |
| **Pb** | DMSA/EDTA | DMPS |
| **As** | DMPS | DMSA |
| **Cd** | EDTA | DMPS |
| **Sb** | DMPS/DMSA | EDTA |
| **Sn** | DMPS,DMSA | EDTA |
| **Tl** | Prussian Blue | DMSA |
| **Al** | EDTA | |
| **Ni** | EDTA | DMPS |
| **W** | DMPS/DMSA | |

Kemper (1990); Aposhian, Toxicol (1995) 97:23-38

# ORAL DMSA PROVOCATION PROTOCOL

**DMSA** (meso-2,3-dimercaptosuccinic acid) is the active compound in an FDA approved pharmaceutical agent for lead detoxification, and has also been used extensively for the detoxification of other metals such as mercury, antimony and arsenic. **DMPS** is another dithiol metal binding agent but is not FDA approved; however it can be compounded for physicians. DMSA has only about ½ the bioavailability of DMPS from the G.I. tract. Studies performed at DDI indicate that oral DMSA challenges yield significantly less Hg in the urine than IV or oral DMPS. Therefore, many physicians use DMPS rather than DMSA as the initial provocation and monitoring agent for assessment of toxic metal burden. For those who elect to use oral DMSA as the provocation agent, the following protocol is provided:

## Protocol for DMSA Provocation Challenge

(1) Stop all **non-essential** medications and multi-mineral supplements 24 hours before administration of DMSA. Fish and shellfish should be avoided for ~1 week prior to the challenge.

*(2) On patient's initial assessment, a first a.m. urine sample should be collected with a separate kit and labeled "pre-provocative". On an empty urinary bladder and empty stomach, administer DMSA at **20-30 mg/kg body weight** (≤ 2 g) as a **single oral bolus dose** (J. Nutr Envir Med 1998; 8, 219-231).*

*(3) All urine should be collected for the following **6 hours**. Food should be withheld for 2 h to ensure efficient absorption of the DMSA. 0.5-1 L of purified water should be consumed during collection. Some patients may experience gas, bloating and/or loose stools with this protocol; such symptoms typically subside within 6 hours of dosing. **Mix the 6-hr. urine specimen well** before taking off the 60 ml aliquot for submission to Doctor's Data for analysis.*

Note: **ONE SIZE DOES NOT FIT ALL!** It is prudent to give patients a trial dose of ≤ 100 mg DMSA prior to the initial challenge.

# IV Ca-$Na_2$-EDTA PROVOCATION PROTOCOL

Calcium Disodium Versonate, or **Ca-$Na_2$-EDTA**(ethylene diamine tetraacetic acid) is an FDA approved chelating agent for the treatment of acute lead poisoning in chidren and adults, but has also been used for the detoxification of other metals such as aluminum, nickel, and cadmium. The ***calcium*** disodium form is FDA approved for lead detoxification; a Mg-$Na_2$-EDTA formulation is used for cardiovascular purposes. It is important to be sure that only **Ca-$Na_2$–EDTA** be administered as a slow push /fast drip as the $Na_2$-EDTA form is *life-threatening* if administered too fast. Patients should be well hydrated prior to administration of Ca-$Na_2$–EDTA.

## Protocol for Ca-$Na_2$-EDTA Provocation Challenge

(1) Stop all **non-essential** medications and multi-mineral supplements 24 hours before and during administration of Ca-$Na_2$–EDTA.
(2) Collect a pre-provocative baseline spot urine sample (preferably first morning void) using a DDI collection kit.
(3) Dosage: 50 mg/kg body weight ($\leq$ 3 g); decrease dose in proportion to degree of compromization in creatinine clearance
(4) Push (5-10 min., 1-5X dilution), or fast drip ($\sim$ 15-30 min.) (in 50-100 cc sterile water; the Ca-$Na_2$-EDTA is extremely hyperosmolar)
(5) Collect all urine for 6 hours using a second DDI kit.
(6) The 6-hr. urine specimen should be mixed well before pouring off 60 mL aliquot for analysis at DDI.

# IV DMPS PROVOCATION PROTOCOL

The following challenge protocol was adapted from the IND clinical trial for Dimaval® (DMPS, Heyltex Corporation), and the Heyltex Scientific Monograph for Dimaval®. The purpose of the DMPS challenge is to assess the levels of toxic metals that have accumulated in the body over time in non-circulating tissue depots. In order to differentiate between acute exposure and chronic retention of metals, it is necessary to compare the levels of metals in urine specimens *before and after* the administration of DMPS.

(1) Before the administration of DMPS have the patient collect a first morning urine specimen. Label the specimen/submittal form to indicate that it is the *pre-provocative* specimen.
(2) Have the patient completely empty bladder.
(3) *Slowly* infuse DMPS (**3**-5 mg/kg BW, not > 250 mg) i.v. over a **10-15 minute** period. Do not mix anything with the DMPS with the possible exception of procaine (1%).
(4) Collect urine for **6** hours. The vast majority of metals are excreted in the urine within the first couple of hours after the administration of DMPS. Compliance to complete urine collection during the first couple of hours is **critical** to ensure accurate assessment. The clock starts at the time of administration.
(5) Encourage consumption of purified water (0.5 –1.0 liters). Mix the post-provocative specimen well prior to taking off the 60 ml aliquot for submission to DDI. Record the total urine volume on the submittal form, and indicate that the specimen is *post-provocation*.

# ORAL DMPS PROVOCATION PROTOCOL

Many physicians are not aware of the availability and utility of oral DMPS. Pharmacokinetic studies of Dimaval® (DMPS by Heyltex) suggest that about 45-60% of orally administered DMPS is absorbed in human subjects and peak urine concentrations of DMPS occur between 2 and 3 hours after oral administration (when taken on an empty stomach). The vast majority of mobilized metals are excreted in the urine in hours 2-4. Thus, a 6-hour post-provocative urine collection is recommended.

**Provocation Protocol**

Several German authors describe oral provocation with DMPS at a flat dose of 300 mg, regardless of the size of the patient. Given that oral DMPS appears to be absorbed at about 50%, it seems logical to dose patients at approximately 2X the IV dose or 500 mg. A commonly used challenge protocol for adults entails oral bolus administration of DMPS at 10 mg/kg body weight (5 mg/kg for children), followed by a **complete** collection of all urine for 6 hr. It is recommended that multi-mineral supplements be withheld 24 hours prior to, and on the day of administration of DMPS. Patients should also be advised to abstain from the consumption of all fish and seafood for one week prior to the provocation test.

(1) Have patient fast for approximately 8 hours.
(2) Empty bladder completely prior to administering DMPS orally at 10 mg/kg ( not to exceed 500 mg).
(3) Encourage consumption of 0.5 to 1 liter of fluids.
(4) Collect ALL urine for the subsequent 6 hours.
(5) If necessary, a light meal (no fish!) may be consumed 2-4 hrs. after administering the DMPS.

# METAL DETOXIFICATION PROTOCOLS

*Nutritional deficiencies and dysbiosis should be resolved **before** beginning detoxification therapy. Creatinine clearance and whole blood or RBC elemental status should be monitored throughout treatment.*

Treatment protocols for heavy metal burden commonly address:

- Therapy to open routes of elimination/ increase excretion
- Mineral supplementation tailored to patient's needs and chelator affinities
- Antioxidant therapy
- Optimization of GI health
- Amino acid supplementation based on patient's needs and general detox support (phase 2 conjugants, cysteine, glutathione precursors)
- Specific nutritional/ therapeutic needs of the patient

It is beyond the scope of this document to cover all of the components of a comprehensive metal detoxification protocol. Following are the basic dosage recommendations of detoxification agents commonly used with treatment protocols. There are also many other protocols and routes of administration. It is at the discretion of the clinician to select the protocol that is right for each patient.

In most protocols multimineral supplementation (in some cases with the exception of Mg) is withheld on days of treatment.

**Intravenous Ca-$Na_2$-EDTA Treatment Protocol**

Assess nutritional Zn sufficiency (Whole Blood Elements), and supplement appropriately before beginning Ca-$Na_2$-EDTA chelation therapy.
Administer IV push/drip as per provocation protocol 1-4x/mo.

**Oral DMSA Treatment Protocol**

A commonly used, effective and well tolerated DMSA treatment protocol entails a two-week cyclical approach:
Three days on DMSA at **10-30 mg/kg total body wt/day** in divided doses, and 11 days off. The total daily dose should NOT EXCEED 2.0 grams, regardless of body weight. Some practitioners find it useful to start at a lower total daily dose, and increase as tolerated. Several practioners report minimal incidence of side effects associated with a dosing protocol that entails 500 mg DMSA, 3X/day for most adults.

## Oral DMPS Treatment Protocol

There are currently no well-established protocols in the literature for the therapeutic use of oral DMPS, although daily and cyclic use has been described.

A commonly utilized cyclic protocol entails 2-3 days on oral DMPS, 11 days off. Dosage varies at 100-200 mg t.i.d. (adults), or 10 mg/kg divided in 3 equal doses per day. Treatment frequency and dosage should be based on the individual case. Patients should be encouraged to consume plenty of fluids throughout treatment.

For details regarding contraindications and potential side effects of DMPS, contact your compounding pharmacist.

## Intravenous DMPS Treatment Protocol

Assess nutritional Cu, Zn, and Mo status (Whole Blood Elements) before and throughout IV DMPS therapy.
Administer IV push/drip as per provocation protocol 1-4x/mo.

## Repeat/ Follow-up Testing

To monitor detoxification therapy, a repeat urine toxic metals should be run after roughly five rounds of treatment or five IV administrations. The original provocation protocol should be repeated, with the same dose, collection period and agent.

# *Toxic Element Chart*

| Element | Sources | Symptoms | Chelator(s) |
|---|---|---|---|
| **Aluminum (Al)** | Beverage cans; pots and pans; foil; metal alloys; water treatment; furnace linings; antacids; antiperspirant; astringents; buffered aspirin; food additives; injectables; dialysis; cosmetics; colloidal mineral products | Pulmonary Disease; Osteomalacia; Neurotoxicity; Suspected cause of Alzheimer's Disease | 1. EDTA |
| **Antimony (Sb)** | Smelters; coal-fired plants; refuse incinerators; tobacco smoke; antihelmithic/antiprotozoal agents; Automobile batteries; solder; sheet metal; pipes; bearings; castings; ammunition; cable sheathing; pewter; semiconductors; aluminum; gallium; infrared detectors; thermoelectric devices; ***Trioxide***: flame retardants; plastics; textiles; rubber, adhesives; paper; pigments; paint; ceramics; pesticides; fireworks | Topical/Respiratory Irritant; Dizziness; HA; Insomnia; Anosmia; HTN; Spontaneous Abortion; Menstrual Disturbances; ECG Abnormalities | 1. DMPS/ DMSA<br>2. EDTA |
| **Arsenic (As)** | Lime manufacturing; automobile batteries; asphalt; asphalt felts and coatings; lead and copper refining (smelters); wood preservative; pesticides(primarily cotton) ; insecticides; herbicides; algicides; growth stimulants for plants and animals; lead oxide; glass; electronics; semiconductors; metallurgy; pigments; electroplating; well water; seafood and shellfish; smog; rodenticides; fungicides | Respiratory/GI Irritant; Lyphocytopenia; Anemia; Birth Defects; Anxiety; Carcinogenic (skin, lung ); Cardiac Arrhythmias; Neurotoxicity; Depression; Garlic Breath; HA; Hyperpigmentation of Skin; Keratosis; Neuralgia/ Neuropathy; PVC's; Spontaneous Abortion; Nephritis | 1. DMPS<br>2. DMSA |
| **Bromine (Br)** | kelp/seaweed, nuts, citrus flavored soft drinks; water purification; pesticides; fumigants; photographic film; dyes; leaded fuel additive; brominated flame retardants: Carpet, upholstery, electronics, mattresses; bromocriptine (hyperprolactinemia), OTC antitussives | GI Inflammation; Asthma; Thyroid Dysfunction; Goiter; HA; Nephritis; Hypotension; Pharyngitis | |
| **Cadmium (Cd)** | Asphalt; asphalt felts and coatings; lime manufacturing; batteries; metal plating; pigments; plastics; paints; | Respiratory/GI Irritant; Nephrotoxicity; Anemia; Bhavioral Changes; Cancer (lung, | 1. EDTA<br>2. DMPS (may |

| | | | |
|---|---|---|---|
| | metal soldering and welding; electroplating; semiconductors; metallurgy; photography; printing; textiles; food-shellfish, liver and kidney meat; cigarette smoke; fertilizer; drinking water; fungicides; rubber; photoconductors | prostate ); Emphysema; HA; HTN; Osteomalacia; Autoimmune Disorders; Immunosuppression; Neurotoxicity; Birth Defects; Infertility | dissociate at kidney if urine not alkalized) |
| **Fluorine (F)** | Toothpaste; fluoridated drinking water; infant formula; processed cereals; non-organic grape juices; wine; beer; soda; tea (higher in decaf); glass etching; Freon/ refrigerants; cockroach insecticide fluoridated salt; non-stick coatings **Rx:** Anesthetics: (Enflurane, Isoflurane & Sevoflurane); fluconazole; fluoroquinolone antibiotics, and linezolid antibiotics, Prozac/fluoxetine, efavirenz, fluorouracil, flurbiprofen, fenfluramine, cerivastatin, paxil, fluvoxamine, astemizole (allergy), cisapride, fluvastatin, fluocinonide & fluocinolone (topical corticosteroids); fluticasone & flunisolide; fluocinolone acetonide (intravitreal implant); fludarabine (antiviral); fludrocortisone; antimalarial drugs | Hypocalcemia; Ligament Calcification (ribs,pelvis); Osteomalacia; Arrhythmias; HA; Neuropathy; Vertigo; Anemia; Respiratory Irritant; Male Reproductive Toxin | |
| **Lead (Pb)** | Lead crystal; pesticides; batteries; sheet lead; solder; pipes; roofing materials; caulking; buckles; petroleum refining; radiation protection; pigments; paints; plastics; ceramics; electrical devices; ballast; tv glass; brass; bronze; gasoline; ammunition; mining; electrical wire insulation; drinking water; fertilizer; candle wicks | GI Symptoms; Colic; Anemia; Neurotoxicity; Neuropathy; Hepatotoxicity, P-450 Enzyme Inh; ECG Abnormalities; Infertility; Gingival Lead Lines; Ototoxicity; Growth Retardation; Developmental Delay; Psychomotor impairment; Fatigue; Anxiety; HA; Immunotoxicity; Cancer | 1. EDTA/ DMSA<br>2. DMPS |
| **Mercury (Hg)** | Thermometers; batteries; fish; Pigments; bactericides; antiseptic creams; skin lightening creams; fireworks; dental amalgams; pesticides; asphalt; agricultural chemical; photography; taxidermy; electrical equipment; electroplating; felt making; textiles; interior paint | Fatigue; Neurotoxicity; Emotional Disturbances; Neuropathy; Altered Libido; Birth Defects; Spontaneous Abortion; Excessive Salivation; Tremors; Irritability; Menstrual Disorders; Autoimmune Disease; Nephritis | 1. DMPS/ DMSA |

| | | | |
|---|---|---|---|
| | before 1990; hemorrhoidal preparations; hospital wastes; waste incineration; paper industry; explosives; fungicides | | |
| **Nickel (Ni)** | Jewelry; coins; stainless-steel; ceramics; pigments; cast iron; batteries; electroplating; metal alloys; electrical circuits; dyes; pesticides; lime manufacturing, asphalt; tobacco smoke; volcanoes; power plants; waste incinerators; diesel exhaust; cocoa; hydrogenated oils | Dermatitis; Respiratory Irritation/ Cancer; Emphysema; Colic; Excessive Salivation; Fatigue; HA; Muscle Pain; Vertigo; Hepato/ Nephrotoxicity; Male Infertility | 1. EDTA<br>2. DMPS |
| **Tin (Sn)** | Antihelminthic drugs, bactericides; brass; bronze; coated wire; colored glass; dental materials; dyes; electronics; fabrics; fencing; fingernail polish; flooring; food canning; fungicide; glass; leather; mining; nuclear reactors; paints; paper; perfumes; pesticides; pewter; pharmaceuticals; pipes; polyurethane foams; rodent repellants; ropes; silicone; silverware; soaps; soft plastics; soldering material; wood preservative; food additives; toothpaste (past); plastics; paints; flame retardants; cosmetics; bleaching agents; rodenticides | Topical/Respiratory/GI Irritant; Pneumoconiosis; Neurotoxicity; Immunosuppression; Photophobia; HA; Impaired Memory; Hepato/ Nephrotoxicity; Behavioral Changes; Vertigo; Anemia; Birth Defects | 1. DMPS/ DMSA<br>2. EDTA |
| **Tungsten (W)** | light bulbs; carbide tools; ammunition; fishing sinkers; golf clubs; ceramic pigments; textile dyes/waterproofing/flame retardants | Topical/Respiratory Irritant, Pneumoconiosis; Lung Cancer; Antagonism of Molybdenum | 1. DMPS/ DMSA |

# Comprehensive Laboratory Analysis

## GASTROINTESTINAL HEALTH

### Comprehensive Stool Analysis
- Optimize digestion and absorption to facilitate assimilation of nutrients
- Identify GI inflammation and immune dysfunction
- Restore microflora balance
- Target treatment of pathogenic yeast, bacteria and parasites with detailed sensitivity information
- Minimize GI derived toxins

### Intestinal Permeability
- Improve barrier function to pathogens
- Maximize nutrient absorption
- Minimize GI absorption of toxins

## NUTRITIONAL STATUS

### Whole Blood/RBC Elements
- Assess essential element status / metal *exposure*
- Used before and during metal detoxification
- Nutritional deficiencies may be due to underlying GI dysfunction

### Amino Acids
- Guides optimization of nutritional status & functional levels of nutrient cofactors ($Mg^{2+}$, $Zn^{+}$, B vitamins, etc.)
- Identify dysbiosis (urine aminos), and necessity of stool testing to target treatment

### Urine Iodide
- Assess Iodine/Iodide sufficiency (essential for thyroid function and breast health)
- Traditional 1st AM or 24 hour, **or** 24 hour "load" test collection options

## TOXIC METAL EXPOSURE

### Hair Elements
- *Exposure* to toxic elements over past 2-4 months
- Negative results do not necessarily rule out net retention

### Water Testing
- Screen for the presence of 17 potentially toxic metals in drinking water plus Fluoride and pH

### Fecal Metals
- Primarily reflects dietary / oral exposure
- Assess amount of mercury exposure from dental amalgams
- Evaluate treatment agents that may increase biliary excretion

## BODY BURDEN/ METAL RETENTION

### Creatinine Clearance
- Assess renal function
- Used prior to provocation challenge, and periodically during therapy

### Pre-provocative Urine Toxic Metals
- Preferably 1st AM void before challenge
- Identify acute / ongoing metal exposure

### Provoked Urine Toxic Metals
- 6-hour collection after provocation
- Comparison to pre-provocative sample permits evaluation of net retention