Dimercaptosuccinic Acid (DMSA), A Non-Toxic, Water-Soluble Treatment For Heavy Metal Toxicity

by Alan L. Miller, N.D.

Abstract

Heavy metals are, unfortunately, present in the air, water, and food supply. Cases of severe acute lead, mercury, arsenic, and cadmium poisoning are rare; however, when they do occur an effective, non-toxic treatment is essential. In addition, chronic, low-level exposure to lead in the soil and in residues of lead-based paint; to mercury in the atmosphere, in dental amalgams and in seafood; and to cadmium and arsenic in the environment and in cigarette smoke is much more common than acute exposure. Meso-2,3-dimercaptosuccinic acid (DMSA) is a sulfhydryl-containing, water-soluble, non-toxic, orally-administered metal chelator which has been in use as an antidote to heavy metal toxicity since the 1950s. More recent clinical use and research substantiates this compound's efficacy and safety, and establishes it as the premier metal chelation compound, based on oral dosing, urinary excretion, and its safety characteristics compared to other chelating substances.
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Introduction

Contamination of water, air, and food by numerous chemicals and non-essential elements, such as heavy metals, is an unfortunate byproduct of a complex, industrialized, high-tech society. The resultant accumulation of heavy metals in the human body poses a significant health risk, leading to a wide array of symptomatology, including anemia, learning deficits, reduced intelligence, behavioral and cognitive changes, tremor, gingivitis, hypertension, irritability, cancer, depression, memory loss, fatigue, headache, hyperuricemia, gout, chronic renal failure, male infertility, osteodystrophies, and possibly multiple sclerosis and Alzheimer's disease.

Although human lead toxicity has decreased in the United States since discontinuation of the use of lead as a gasoline additive, it continues to be a significant problem, especially in urban areas, where lead-based paint exposure is still an issue, and in areas where lead is mined and/or smelted. Chronic mercury toxicity from occupational, environmental, dental amalgam, and contaminated food exposure, is a significant threat to public health. Other heavy metals, including cadmium and arsenic, can also be found in the human body due to cigarette smoke, and occupational and environmental exposure. Diagnostic testing for the presence of heavy

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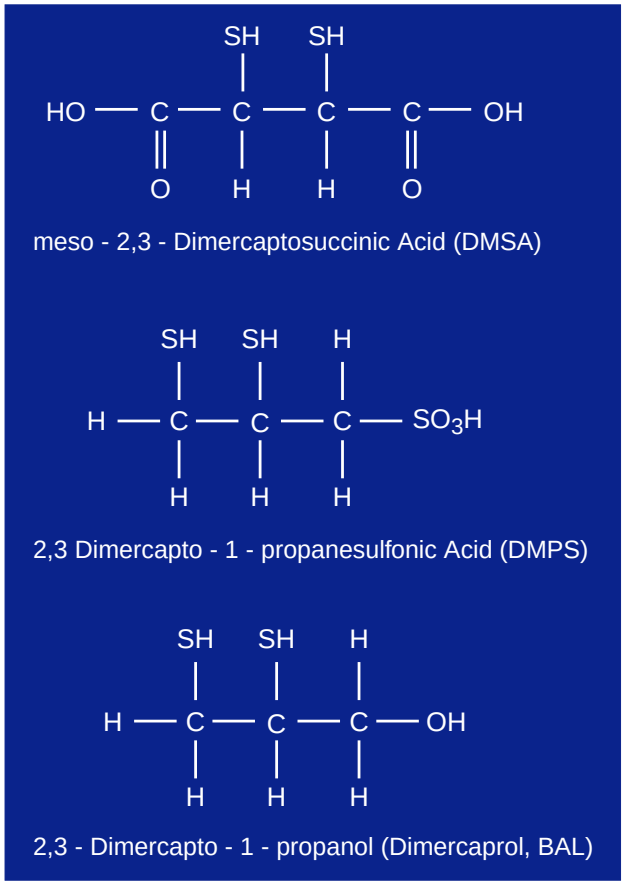
Figure 1.



metals, and subsequently decreasing the body's burden of these substances, should be an integral part of the overall treatment regimen for individuals with the above-mentioned symptomatology or a known exposure to these substances.

It has long been acknowledged that sulfhydryl-containing compounds have the ability to chelate metals. The sulfur-containing amino acids methionine and cysteine, cysteine's acetylated analogue N-acetylcysteine, the methionine metabolite S-adenosylmethionine, alpha-lipoic acid, and the tri-peptide glutathione (GSH) all contribute to the chelation and excretion of metals from the human body.

Meso-2,3-dimercaptosuccinic acid (DMSA), is a water-soluble, sulfhydryl-containing compound which is an effective oral chelator of heavy metals. Initial studies over forty years ago identified DMSA as an effective antidote to heavy metal poisoning. DMSA was subsequently studied for twenty years in the People's Republic of China, Japan, and Russia before scientists in Europe and the United States "discovered" the substance and its potential usefulness in the mid-1970s.[1]

DMSA is a dithiol (containing two sulfhydryl, or S-H, groups) and an analogue of dimercaprol (BAL, British Anti-Lewisite), a lipid-soluble compound also used for metal chelation (see Figure 1). DMSA's water solubility and oral dosing create a distinct advantage over BAL, which has a small therapeutic index and must be administered in an oil solution via painful, deep intramuscular injection.[2] DMSA, on the other hand, has a large therapeutic window and is the least toxic of the dithiol compounds.[3]

Lead

Lead exposure is still a public health problem in the United States, being found in approximately 21 million pre-1940 homes. Dust and soil lead, derived from flaking, weathering, and chalking paint, also contribute to chronic exposure.

Lead competes in the body with calcium, causing numerous malfunctions in calcium-facilitated cellular metabolism and calcium uptake and usage, including inhibition of neurotransmitter release and blockade of calcium channels and calcium-sodium ATP pumps.

The central nervous system (CNS) appears to be affected the greatest by lead. Children in particular are susceptible to its devastating effects on mental development and intelligence. Neurobehavioral deficits resembling attention deficit disorder have also been found in lead-exposed children.[4] Blood lead concentrations of 20-25 µg/100 ml can cause irreversible CNS damage in children.[5]

Poor quality nutrition, including deficiencies in iron and calcium, are known to exacerbate the manifestations of lead exposure, including its CNS effects. Acute adult lead exposure leads to renal proximal tubular damage; chronic exposure causes renal dysfunction characterized by hypertension, hyperuricemia, gout, and chronic renal failure.[6]

Inorganic lead is absorbed, distributed, and excreted. Once in the blood, lead is distributed primarily among three compartments – blood, soft tissue (kidney, bone marrow, liver, and brain), and mineralizing tissue (bones and teeth). Mineralizing tissue contains about 95 percent of the total body burden of lead in adults.

After lead is absorbed in the human body, it reacts with thiol (sulfhydryl) groups on peptides and proteins, inhibiting enzymes involved in heme synthesis and interfering with normal neurotransmitter functions.[7] This natural reaction with thiols is also the body's method of eliminating lead, especially from the liver. Hepatic glutathione attaches to lead and enhances its excretion in the feces. Unfortunately, hepatic glutathione can be depleted in this manner, resulting in less glutathione being available for conjugation of other toxic substances. In addition to these hepatic effects, individuals with higher concentrations of blood lead have been noted to have lower levels of erythrocyte reduced glutathione.[8] Decreased erythrocyte glutathione is due to the fact that 99 percent of lead in the blood is attached to red blood cells; the remaining one percent is in the plasma. Lead stored in bone has a half-life of 25 years, although lead in bone can be mobilized into the blood, and subsequently to other tissues.

Mercury

Humans are exposed to mercury primarily in two forms: mercury vapor and methyl mercury compounds. Unfortunately, mercury is a ubiquitous substance in our environment. Mercury vapor in the atmosphere makes its way into fresh and salt water by falling in precipitation. Methyl mercury compounds are created by bacterial conversion of inorganic mercury in water and soil, which subsequently concentrates in seafood and fish. Dietary fish intake has been found to have a direct correlation with methyl mercury levels in blood and hair.[9,10]

"Silver" amalgam dental fillings are the major source of inorganic mercury exposure in humans.[11] This term, however, is a misnomer, as this compound is not predominately silver; the proper term should be "mercury amalgam." The most common dental filling material, amalgams contain approximately 50 percent liquid metallic mercury, 35 percent silver, 9 percent tin, 6 percent copper, and a trace of zinc.[12] As they are prepared and placed in the patient's mouth, the dentist and the person preparing the amalgam,[13,14] as well as the patient are exposed to mercury vapor (HgO).

Clinical studies indicate DMSA is a safe and effective means of decreasing the body burden of these metals.

Lead	Arsenic
Mercury	Cadmium

The patient is further exposed to mercury vapor as the amalgam releases HgO when the individual chews,[15-17] brushes,[18] or drinks hot beverages.[16-18] Studies of mercury content in expired air of those with and without amalgams have found significantly higher baseline mercury levels in subjects with amalgams, and

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up to a 15.6-fold increase in mercury in expired air after chewing.[15,16] Mercury release was found to be greater in corroded amalgams compared to new, polished fillings.[18] Mercury vapor from amalgams enters the bloodstream after being inhaled into the lungs.

Comparisons of blood levels of mercury and the number of amalgams show a direct correlation between number of amalgam fillings and concentration of blood[17,19] and urine mercury.[13,14,20] In addition, a statistically significant correlation was found between the number of dental amalgam fillings and mercury content of the kidney cortex ($p < 0.0001$) and the occipital lobe cortex of the brain ($p < 0.0016$) in cadavers.[21]

After removal of all amalgams, there is a transient increase in mercury concentration in the blood, plasma, and feces, followed by a decrease in blood levels below the pre-removal baseline.[11,19,22,23]

Mercury vapor is lipid soluble, freely passing through cell membranes and across the blood-brain barrier. Methyl mercury also easily crosses the blood-brain barrier and the placenta.[7] Inorganic and methyl mercury have a high affinity for sulfhydryls, reacting intracellularly with the sulfhydryl group on glutathione and cysteine, and histidine residues in proteins, and allowing transport out of the cell. In rats, it was found that mercury secretion into the bile was dependent on glutathione secretion into the bile, suggesting the biliary secretion of mercury is in large part dependent on the biliary transport of GSH.[24-26] In humans, 90 percent of mercury elimination is via the feces, with only 10 percent normally being excreted in the urine.[12] A decrease in hepatic glutathione content secondary to excretion of mercury can decrease hepatic cell viability by mechanisms stated earlier.

Arsenic and Cadmium

Environmental arsenic and cadmium exposure comes from pollutants discharged from industries utilizing these metals, including herbicide and battery manufacturers. These metals are also found in cigarette smoke.

Cadmium, as well as lead and mercury, can interact metabolically with nutritionally essential metals. Cadmium interacts with calcium in the skeletal system to produce osteodystrophies, and competes with zinc for binding sites on metallothionein, which is important in the storage and transport of zinc during development.

Biliary excretion seems to be an essential factor for the fecal elimination of cadmium and arsenic, although these metals may be also excreted in the urine.[27,28]

Pharmacokinetics of DMSA

In healthy individuals, approximately 20 percent of an oral dose of DMSA is absorbed from the gastrointestinal tract. Ninety-five percent of the DMSA that makes it to the bloodstream is bound to albumin. Most likely, one of the sulfhydryls in DMSA binds to a cysteine residue on albumin, leaving the other S-H available to chelate metals. In healthy fasting men, 90 percent of the DMSA recovered in the urine was found to be mixed disulfides of DMSA (DMSA attached to one or two cysteine molecules), and 10 percent was free unchanged DMSA. No mixed disulfides were found in the blood.[29-31] It is thought these are formed as albumin releases DMSA in the kidney.[32]

In three children with lead poisoning, free DMSA was found in the blood of all subjects, while it was found in only one out of five healthy adult subjects. It is not known

whether this is an age-related phenomenon, or exactly what the significance of this finding might be. It is unknown if these pharmacokinetic parameters are different in other metal toxicities or concomitant disease processes. For instance, if the patient has increased gut permeability, does this increase DMSA absorption?

Studies addressing the possibility that DMSA may chelate metal stored in the gut, because a significant percentage of an oral dose is not absorbed, have yet to be done. A study of whole body retention in mice of radioactively-tagged, orally-administered mercuric chloride revealed DMSA and its analogue DMPS (2,3-dimercaptopropanesulfonate) (see Figure 1), given orally at the same time as the mercury, significantly decreased the absorption and whole body retention of the metal.[33] This is an important finding which suggests administration of DMSA a short time after an acute ingestion of mercury will chelate the metal and decrease the amount absorbed. It does not, however, answer the question of whether DMSA will bind gut reservoirs of mercury or whether it will assist the liver in elimination of mercury due to chronic exposure.

DMSA Treatment in Lead Toxicity

DMSA has been used since the 1950s as an antidote for lead poisoning in Russia, Japan, and the Peoples Republic of China. DMSA has been shown in recent studies to be a safe and effective chelator of lead, reducing blood levels significantly.[1,34,35] At a dose of 10 mg/kg for five days in adult males, DMSA lowered blood lead levels 35.5 percent; a more aggressive approach utilizing a 30 mg/kg dose lowered blood lead 72.5 percent. Clinical symptoms and biochemical indices of lead toxicity also improved.[35]

An animal study indicated DMSA is an effective chelator of lead in soft tissue, but it may not chelate lead from bone.[36] Another found DMSA or calcium disodium ethylenediamine tetraacetic acid ($CaNa_2EDTA$) produced significant reductions in kidney, bone and brain lead levels, but DMSA produced greater reductions of bone lead.[37]

In a preliminary animal study, combination therapy with DMSA and $CaNa_2EDTA$ was more effective than either individual chelator at increasing urinary and fecal elimination of lead, and reducing hepatic, renal, and femur lead concentrations in rats.[38]

It has been suggested that chelating agents, including BAL and $CaNa_2EDTA$, may mobilize and redistribute lead to soft tissue, including the brain. Lead-exposed rats given $CaNa_2EDTA$ showed an initial decrease in bone and kidney lead, and an increase in hepatic and brain lead concentrations, indicating redistribution to these organs.[39] Rats administered DMSA in combination with $CaNa_2EDTA$ showed increased urinary lead output and decreased tissue burden versus use of these therapeutic substances individually. No redistribution of lead to the brain was observed with the combined therapy. A decrease in blood zinc level was noted with the combination, as has been observed with $CaNa_2EDTA$ monotherapy.[40]

In a study of lead's pro-oxidant activity and the effect of thiol substances as antioxidants, five weeks of lead exposure in mice depleted hepatic and brain glutathione (GS) levels, and increased malondialdehyde (MDA), a marker of lipid peroxidation. DMSA administration for seven days resulted in a reduction in blood, liver, and brain lead levels. N-acetylcysteine supplementation decreased MDA levels, indicating amelioration of oxidative stress by NAC, but it did not decrease lead levels.[41]

In an animal study, co-administration of ascorbic acid (vitamin C) with DMSA enhanced the urinary excretion of lead in rats compared to DMSA alone.[42]

A suggested protocol for lead toxicity is to identify and remove the environmental exposure, and use DMSA 10 mg/kg three times a day for the first five days, followed by 14 days at 10 mg/kg twice a day.

DMSA Treatment in Mercury Toxicity

DMSA has been in recent use as a treatment for mercury poisoning since Friedheim reported on DMSA treatment of experimental toxicity in mice in 1975, noting its low toxicity and favorable efficacy compared to BAL and D-penicillamine.[43] Since that time, numerous animal and human studies have shown DMSA administration increases urinary mercury excretion and reduces blood and tissue mercury concentration.[3,33,44-47]

In a comparison study of chelating agents, eleven construction workers with acute mercury poisoning were treated with either DMSA or N-acetyl-D,L-penicillamine (NAP), another sulfhydryl-containing metal chelator. DMSA treatment resulted in greater urinary excretion of mercury than NAP.[48]

In a study of single-dose, DMSA-induced urinary excretion in occupationally-poisoned workers, a significant increase in urinary mercury excretion was noted, especially in the first 24 hours. Mercury excretion was greatest in the first eight hours after oral DMSA administration.[49]

After methylmercuric chloride administration in rats, DMSA, DMPS, and NAP were studied for their ability to remove mercury from blood and tissue. DMSA was the most effective at removing mercury from the blood, liver, brain, spleen, lungs, large intestine, skeletal muscle, and bone. DMPS was more effective at removing mercury from the kidneys.[50]

Chelation of Mercury from the Brain

In rats, following intravenous administration of methyl mercury, DMSA was found to be the "most efficient chelator for brain mercury."[51]

In another animal study, DMSA was given four days after methyl mercury injection in mice, and continued for eight days. DMSA removed two-thirds of the brain mercury deposits, NAP removed approximately one-half, while DMPS did not remove significant amounts of mercury from the brain.[44]

DMSA has also been used effectively in arsenic and cadmium poisoning.[2,3,52]

Mercury Diagnostic and Treatment Protocol

Hair analysis is an inexpensive and valuable tool for evaluating prior mercury exposure.[10,53] An effective way to evaluate mercury toxicity quantitatively is to determine the amount of mercury excreted in the urine after a challenge dose of DMSA. A baseline 24-hour urine is collected before the challenge, then again on day three of a three-day dosing of 200 mg three times a day.

The therapeutic dosage of DMSA for mercury toxicity is not well defined in the literature. Doses as high as 30 mg/kg per day have been used, with no serious side effects noted.[34] One DMSA treatment protocol suggests 10 mg/kg day taken in divided doses for three days. The patient then discontinues taking DMSA for 14 days, then takes it again for 3 days. Five to 10 treatment cycles may be necessary.[54] Another protocol suggests 500 mg per day on an empty stomach, every other day for a minimum of five weeks. For very sensitive patients, 250 mg per day, every other day may be necessary, with an increase to 500 mg after two to three weeks, for a total of five weeks of therapy.[55] More studies need to be done to define optimal dosing strategies for

this substance. Be aware that sulfhydryl compounds in DMSA will make urine smell very sulfurous. Adequate communication with the patient regarding this issue is important, so they are not taken by surprise.

Adjunctive nutrient therapy includes hydrolyzed whey protein, as it contains cysteine and cysteine residues which can be of benefit while using DMSA. Cysteine is the rate-limiting step in glutathione production, necessary for fecal heavy metal excretion and hepatoprotection. Whey also contains branched-chain amino acids, which will occupy transport sites at the blood-brain barrier, effectively keeping bound metals from being re-deposited in the brain. Supplemental dosing of N-acetylcysteine, 500 mg three times per day, can also be helpful.[54] A multi-mineral supplement can be taken between cycles.

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