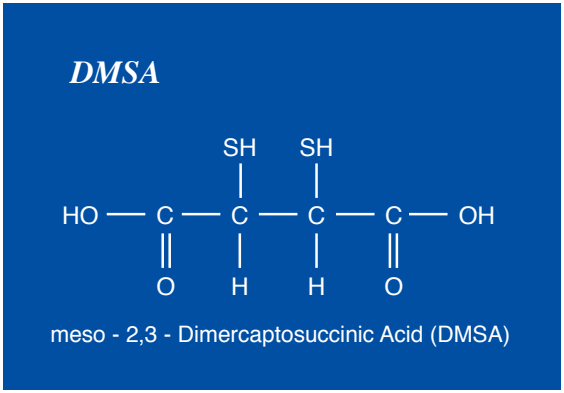

Meso 2,3-Dimercaptosuccinic Acid (DMSA)

Introduction

Contamination of water, air, and food by chemicals and heavy metals is an unfortunate consequence of our 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 and disease states. Although environmental lead levels have decreased in the United States since lead was eliminated from gasoline and lead-based paint, lead continues to be a significant problem, particularly in urban areas and areas of lead mining and smelting. In addition, mercury, cadmium, and arsenic toxicity from occupational and environmental exposure also continue to pose significant threats to public health. For these reasons, diagnostic testing for heavy metals and the subsequent decrease in the body's burden of these substances has become a necessity. Meso-2, 3-dimercaptosuccinic acid (DMSA) is a sulfhydryl-containing, water-soluble, non-toxic, orally administered, metal chelator[1] which has been in use as an antidote to heavy metal toxicity since the 1950s. DMSA's water solubility, oral dosing, large therapeutic window, and low toxicity[2,3] make it superior to other chelating agents available.

Pharmacokinetics and Mechanism of Action

The ability of sulfhydryl-containing compounds to chelate metals is well established. 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. Approximately 20 percent of an oral dose of DMSA is absorbed from the gastrointestinal tract of healthy individuals. Ninety-five percent of the DMSA that makes it to the bloodstream is bound to albumin. It is suggested that one of the sulfhydryls in DMSA binds to a cysteine residue on albumin, leaving the other S-H available to chelate metals.[4,5] DMSA and other dithiol agents have a binding affinity for lead, mercury, cadmium, arsenic, bismuth, tin, nickel, and thallium.[6] Studies indicate the half-life of oral DMSA is approximately three hours, with up to 70 percent of an oral dose eliminated in the first six hours.[7,8] Over 90 percent of DMSA found in urine is in a mixed disulfide form, in which one or two cysteine molecules are attached to each DMSA molecule.[5]

Clinical Indications

Lead Toxicity

Lead exposure continues to be a public health problem in the United States. Lead- containing paint is still found in millions of pre-1940s homes. Lead toxicity causes numerous malfunctions in calcium uptake and utilization, and also interferes with calcium-facilitated cellular metabolism. Lead is particularly toxic to the central nervous system (CNS), as evidenced by its particularly deleterious effects on mental development and intelligence in children with lead toxicity. In addition, neurobehavioral deficits resembling attention deficit disorder have been attributed to lead exposure.[9] In a child, blood lead concentrations of 20-25 mg/100 ml can cause irreversible CNS damage.[10] In adults, acute lead exposure leads to renal proximal tubular damage, while chronic exposure causes renal dysfunction characterized by hypertension, hyperuricemia, gout, and chronic renal failure.[11] DMSA has been shown to be successful in lowering blood lead levels in children[12,13] and adults[14,15] with lead toxicity, and is FDA approved for use in chelation of lead in children.

Mercury Toxicity

Human exposure to mercury is primarily in two forms: mercury vapor and methylmercury compounds. Mercury vapor in the atmosphere makes its way into fresh and salt water by falling in precipitation. Methylmercury compounds are created by bacterial conversion of inorganic mercury in water and soil, and are subsequently concentrated in seafood. Dietary fish intake has been found to have a direct correlation with methylmercury levels in blood and hair.[16,17] "Silver" amalgam dental fillings (which are approximately 50-percent mercury) are the major source of inorganic mercury exposure in humans.[18] Mercury vapor is released as the individual chews[19] or drinks hot beverages,[20] and is inhaled, resulting in increased blood mercury levels. Studies have shown a direct correlation between the number of amalgam fillings and concentration of blood[21] and urine mercury.[22]

DMSA is an effective mercury chelator,[23] and when compared to treatment with other chelating agents, results in the greatest urinary excretion of mercury,[24] It is the most effective at removing mercury from the blood, liver, brain, spleen, lungs, large intestine, skeletal muscle, and bone.[25] In animal studies following intravenous administration of methylmercury, DMSA was the "most efficient chelator for brain mercury,"[26] removing two-thirds of brain mercury deposits.

Cadmium and Arsenic Toxicity

Environmental cadmium exposure comes from pollutants discharged by industries utilizing it, including herbicide and battery manufacturers. It is also found in cigarette smoke. Cadmium, like lead and mercury, can interact metabolically with essential minerals. 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. Cadmium poisoning can lead to rhinitis, nephropathy, and osteomalacia, and has a possible link to cardiomyopathy, hypertension, and hepatic and prostate disorders.[6,27]

Arsenic toxicity is also usually a result of exposure to industrial pollutants or cigarette smoke. Symptoms include eczema, dermatitis, malaise, muscle weakness, and "garlic breath."[14] The use of DMSA in arsenic chelation is more effective in cases of acute poisoning than in those of long-term exposure. This may be due, in part, to the possibility that DMSA is a more effective chelator of arsenic in the bloodstream than it is of the tissue-bound arsenic seen in long-term exposure.[14]

Side Effects and Toxicity

DMSA is very safe and generally well tolerated, with few side effects being noted. Some patients may experience slight gastrointestinal disturbances or urticaria, but it is not usually necessary to discontinue treatment.[28] Rare cases of a rash (which resolves upon discontinuation of DMSA) developing after two or three rounds of treatment have been reported. Any detoxification regimen requires the bowels to be fully functioning. If a patient is constipated, normal bowel function should be restored prior to DMSA chelation. DMSA can chelate other elements, including copper, manganese, molybdenum, and zinc, which might result in deficiencies. Although DMSA does not directly bind magnesium, cysteine, and glutathione, heavy metal detoxification can result in depletion of these nutrients as well.[6] Therefore, deficiencies of these essential elements should be screened for and corrected. Sulfhydryl compounds in DMSA can make urine smell very sulfurous, necessitating adequate communication with the patient regarding this issue.

Dosage

DMSA can be used, via an oral challenge and urinary analysis, to diagnose heavy metal toxicity. 500 mg is given per day, in divided doses between meals, for three days. During the third day the urine is collected for 24 hours. A sample is taken from the total amount and sent to a laboratory. An alternate method suggested by some labs is a 20-30 mg/kg body weight dosage, taken in one dose on an empty stomach, and urine is collected for six hours. A sample is then sent to the lab to be analyzed.

Dosing protocols for heavy metal toxicity treatment using DMSA vary depending on physician preference and individual patient need, but currently two protocols are most often used. In one protocol, 10-30 mg/kg body weight is given per day in three divided doses, using a three-days-on, 11-days-off cycle, with a minimum of eight cycles. A second protocol involves giving 500 mg per day (in two or three divided doses) every other day for a minimum of five weeks. DMSA appears to be absorbed best when taken between meals.[29]

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