Heavy Metal Toxicity and Chelation Therapy

Dr. Anubha Sharma
Associate Professor - Chemistry
Govt. Auto. Girls P.G. College of Excellence, Sagar (M.P.)

Abstract

Heavy metals are defined as those elements with a high (>5.0) relative density. Heavy Metal toxicity refers to an overexposure to lead, mercury, arsenic, cadmium, chromium or other high density element that causes irritation or damage to the body.Chelation therapy with chelating agents like calcium disodium ethylenediamine tetra acetic acid ($CaNa_2$ EDTA), British Anti Lewisite (BAL), sodium 2,3-dimercaptopropane 1-sulfonate (DMPS), meso 2,3-dimercaptosuccinic acid (DMSA) *etc.*, is considered to be the best known treatment against metal poisoning. Newer strategies like combination therapy (use of structurally different chelating agents) or co-administration of antioxidants are also being studied nowadays to address various side effects of chelating agents.

Key words : Chelation, combination therapy, antioxidants.

Introduction

Toxic metals are dispersed in the environment through industrial effluents, organic wastes, refuse burning and power generation. The impact of these toxic agents on human health is currently an area of intense interest.There are two types of health hazard: (1) hazards with a threshold for the relationship between exposure and the health effect (most target organ effects) and (2) hazards with nonthreshold effects considered to pose some level of risk at any level of exposure (cancer and mutagenic effects). The five transition metals—arsenic, cadmium, chromium VI, beryllium, and nickel—are accepted as human carcinogens in one form or another. The toxic manifestations of these metals are caused primarily due to imbalance between pro-oxidant and antioxidant homeostasis which is termed as oxidative stress.

Toxicities of Various Heavy Metals

Arsenic

Oral ingestion of a single high dose (300 mg) can be fatal to an adult. Single or repeated oral high doses (0.04 mg/kg/day) for weeks or months can produce gastrointestinal effects such as diarrhea and cramping, anemia, and leucopenia, peripheral neuropathy, used for treatment are solution of hydrated ferric oxide or Dimercaprol (BAL).

Lead

Metallic lead and its salts like lead carbonate,lead acetae,lead monoxide etc. are poisonous.Toxicity manifests as facial pallor, anaemia with basophilia, colic and

constipation and neuropathy. Adults with high blood lead levels (greater than 40 µg/dL) may have impaired heme synthesis and chronic kidney disease (blood lead levels above 60 µg/dL). Diagnosis is done by blood and urine levels of lead,protoporphyrin level in blood and coproporphyrin level in urine. Chelation is done by using Succimer or EDTA.

Cadmium

High exposure to cadmium can cause acute bronchitis,emphysema or pulmonary fibrosis and lung cancer. Chronic exposure over several years to low doses of cadmium— which might occur through cigarette smoking or daily ingestion of cadmium contaminated rice—can cause kidney tubular dysfunction and osteoporosis.

Mercury

The toxicity of elemental mercury is due to mercuric mercury. Effects include tremor, psychiatric disturbances, and altered behaviour, glomerulnephritis. Exposure to methyl mercury follows the consumption of fish that have accumulated methyl mercury from the aquatic food chain. Methyl mercury readily crosses the placenta resulting in toxicity to the developing brain, impaired development of motor and language skills, blindness, deafness. Chelating agent of choice is BAL.

Copper

The major sources of environmental copper releases include the mining, smelting and refining of copper, industries producing products from copper. Acute poisoning can cause gastrointestinal symptoms such as nausea, vomiting, and abdominal pain. Liver toxicity was seen in doses high enough that resulted in death. Eyes show chalcosis lentis.Vineyard Sprayer Lung disease refers to development of granulomas in lung following copper toxicity. Detecting copper levels in blood and urine helps in diagnosis. Treatment is done by administering BAL and oral Penicillamine.

Nickel

Nickel fumes are respiratory irritants and may cause pneumonitis, respiratory failure, pulmonary embolism, asthma and bronchitis.

Chelation in Metal Toxicities

The Greek word '*Chele*' means claw of a lobster, thus the term CHELATION explains the concept of clinging or holding with a strong grip. Chelating agents bind to toxic metal ions to form complex structures which are easily excreted from the body. Chelating agents possess "ligand" binding atoms that form either two covalent linkages or one covalent and one co-ordinate or two co-ordinate linkages in the case of bidentate chelates. Mainly atoms like S, N and O function as ligand atoms in the form of chemical groups like –SH, –S-S, –NH2, =NH, –OH or >C=O. Bidenate or multidentate ligands form ring structures that include the metal ion and the two-ligand atoms attached to the metal.

Dimercaprol (also named British Anti-Lewisite or BAL) was developed as an antidote against the arsenic-based poison gas Lewisite. However, BAL is not an ideal

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chelator due to its high frequency of various side effects. Increased brain deposition due to BAL administration has been reported for arsenite and organic mercury compounds.BAL was modified into meso 2,3-dimercaptosuccinic acid (DMSA), a related dithiol with fewer side effects. Another dithiol, sodium 2,3-dimercaptopropane 1-sulfonate (DMPS), was introduced as a mercury-chelating agent.

Desferrioxamine (DFOA), an iron chelator, completely covers the surface of Fe^{+3} during complex formation, thereby preventing iron-catalyzed free radical reactions but Ethylenediamine-tetraacetic acid (EDTA) is not able to shield the surface of the Fe^{+3} ion, but forms an open complex (basket complex), thereby increasing the catalytic capacity of Fe^{+3} for generating oxidative stress.

Calcium disodium ethylenediamine tetraacetic acid ($CaNa_2EDTA$) is the most commonly used chelating agent. It is a derivative of ethylenediamine tetraacetic acid (EDTA). It has been one of the main stays for the treatment of childhood lead poisoning. In addition to urinary excretion of lead, $CaNa_2EDTA$ is responsible for the excretion and depletion of essential metals like Zn, Cu, Fe, Co and Mn because of its relative lack of specificity.

For ions such as Pb^{+2}, Hg^{+2}, Cd^{+2} and As^{+3}, thiolates and amines are the preferred ligands. Also, the sulfur-containing amino acids methionine and cysteine, *N*-acetylcysteine, the methionine metabolite *S*-adenosylmethionine, α-lipoic acid, and the tripeptide glutathione (GSH) all contribute to the chelation and excretion of metals from the human body.

New Chelating Agents

Some mono and diesters of DMSA have been tried against cases of experimental heavy metal poisoning. Monoisoamyl ester of DMSA (MiADMSA; a C5 branched chain alkyl monoester of DMSA) has been found to be the most effective. *Monomethyl DMSA (MmDMSA) and monocyclohexyl DMSA (MchDMSA)* have better lipophilic characteristic and might penetrate cells more readily than extra-cellularly acting chelating agent like DMSA.

Conclusion

The treatment with these chelating agents is compromised with number of serious side-effects. Studies show that supplementation of antioxidants along-with a chelating agent prove to be a better treatment regimen than monotherapy with chelating agents. Antioxidants are substances, which inhibit or delay oxidation of a substrate while present in minute amounts. They regulate the expression of genes and signal regulatory pathways. Vitamin E (α-tocopherol) is one of the most potent endogenous antioxidants. Vitamin C acts as a scavenger of free radicals.Beta-Carotene has properties similar to vitamin E. Its conjugated double bonds are also responsible for good anti-oxidative

property. Supplementation of ascorbic acid and α-tocopherol has been known to alter the extent of DNA damage. Thus, vitamins supplementation will have sustainable curative value among the already affected populations, neutralizing impact on freshly emerging metal poisoning scenario and possible proactive protection to those potentially susceptible to heavy metal exposure.

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