ROLE OF ESSENTIAL TRACE MINERALS ON THE ABSORPTION OF HEAVY METALS WITH SPECIAL REFERENCE TO LEAD.

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ABSTRACT

Heavy metals are important toxicants known to exert adverse effects in humans and animals, given sufficient exposure and accumulation in the body. This has a great concern both at personal and public health risk. Heavy metals are also known to interact with the essential trace minerals at the level of absorption and also during the metabolism. The adverse effects of the absorbed and accumulated heavy metals include neurological, reproductive, renal and hematological systems. Children are more sensitive than adults to the effects of lead. Efforts are made to understand the mechanism of the interactions of heavy metals with essential trace minerals at the level of absorption. With available sensitive and specific methodologies like Anodic Stripping Voltammetry for the evaluation of the levels of toxic heavy metals such as lead, cadmium, mercury etc., better understanding of heavy metal absorption is made possible.

Due to the poor nutritional standards, risk of heavy metal exposure is still a major concern in developing countries. Studies carried out by the author have provided evidence towards the understanding of the prevailing mechanisms of metal-metal interaction at the intestinal level. During growth and development the demand for the essential minerals being at higher level, differentiation of various essential metals and heavy metals pose an inherent problem due to certain common properties shared by them. With this approach to the problem of heavy metal toxicity, it is preventable not only with environmental intervention but also by the nutritional management.

KEY WORDS

Lead poisoning, lead absorption, toxic metal and essential metal interaction, prevention of lead poisoning, nutritional management of lead poisoning.

INTRODUCTION

Amongst known toxic heavy metals, "Lead" in any form seems to be a ubiquitous environmental poison to any form of life (1). Cadmium and mercury are the other toxic heavy metals causing health hazards in isolated communities exposed due to occupational or economic reasons. Though man has been using lead for a very long time, usage of this metal increased during industrialization resulting in serious health hazards. Lead being a toxic element with no beneficial effects to the human

body occurs in the earth's crust in the form of galena or lead sulfide and is the main source of lead in variety of forms for various purposes (2-4). The softness, malleability, low melting point, resistance to corrosion, ability to make metal carbon compound, low cost and easy workability has made lead a very useful metal. Lead can not be broken down nor is it biodegradable. The most common sources of lead and subsequent lead exposure are through leaded gasoline. Tetraethyl lead used as an antiknock during the manufacturing of gasoline is the main source of lead found in the emission of vehicles getting into air. Apart from this communities living in and around lead based industries that use and emit lead into the environment are at higher risk for exposure of lead (5, 6). Lead in the air is also deposited on the ground and remain in street and house dust, soil and sediments and becomes

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the continuing source of lead exposure. Apart from this, lead is also found in food or drink from cans with lead solder, ceramics with lead glazes, and lead in paints, traditional medicines, folk medicines and cosmetics (7,8). Lead paints continue to be the major source in many developed countries especially causing child hood lead poisoning (9). It is found that in Mexico, Central America and in Asia, ceramics with lead glazes are significant source of lead exposure (10-13). Continuing exposure to lead results in increased absorption and retention of lead in most of the organs. Young children are at greater risk from lead exposure as their bodies and CNS are still developing; their hand to mouth activity is high apart from their greater ability to absorb lead when ingested (14-18). Though lead poisoning is seen in people irrespective of age, race, religion, geographic region and socio economic levels, children seem to be the most affected and *"it is a terrible thing to waste a child"* as the IQ of a child will be adversely affected even at very low levels of blood lead (10 µg/dl). No level in blood is considered safe or normal.

LEAD ABSORPTION, BIOCHEMICAL AND TOXICOLOGICAL EFFECTS

Lead, having no beneficial role to a human enters the body through multiple routes and gets distributed and stored in almost every organ resulting in the defective functions of the organ (19-24). Some appreciable amount of absorbed lead is excreted by the kidneys to an extent of 76%, through gastro intestinal tract to an extent of 16% and to a small extent of around 8% is eliminated by hair, nails, sweat, exfoliated skin, etc (25). Findings of biochemical and toxicological effects of lead studies in detail by many workers have indicated deleterious effects to hematopoietic, renal, neurological, reproductive, and skeletal system (26-31). The hematological effects of lead resulting in mild, hyper, chronic or microcytic anemia are due to the combined effects of reduced hemoglobin production apart from the reduced life span of circulating erythrocytes.

In this regard the below mentioned laboratory diagnosis at biochemical level is recommended.

Assay in urine recommended are:

1. PBG screening
2. ALA quantitation

3. PBG quantitation

Urine and fecal and whole blood, plasma analysis for

1. Total porphyrin
2. Porphyrin fractionation

In the whole blood protoporphyrin fractionation, in the plasma porphyrin-protein complex levels in the RBC, enzymes such as ALA dehydratase, PBG deaminase, uroporphyrinogen cosynthase, uroporphyrinogen decarboxylase and lymph levels of coproporphyrinogen oxidase and ferrochelatase seem to be of great significance.

Effects of lead on renal system are studied in detail. Dysfunctions of proximal renal tubules (Fanconi Syndrome) manifested by glycosuria, generalized amino aciduria, hyperphosphaturia, hypophosphataemia and rickets are noted in acute lead poisoning. Occurrence of nephropathy in the later part of life due to early exposure to lead during childhood is yet to be validated. Long term exposure to lead is known to cause irreversible functional and morphological changes which include interstitial fibrosis, tubular atrophy and ultra-structural changes in renal tubular mitochondria (32). Neurological effects are well understood in the past and CDC's current prevention strategies are centered around the effect of lead on the cognitive and behavioral development of the CNS in the early developing phase of life. Other recognized effects of lead are encephalopathy characterized by ataxia. Lowering of IQ in children even at low lead levels in blood is well documented by Needleman and coworkers(33-35). Detailed understanding of many biochemical indicators used in the diagnosis of lead toxicity at various levels of exposure has provided good laboratory diagnosis of early incidence of lead poisoning.

In the reproductive system, quality of the sperm is also under the influence of body burden of lead. Premature delivery and malformed child are some of the common effects caused by maternal lead. It is well established that the male reproductive system is affected when the blood lead is in the range of 30-40 µg/dl though WHO guidelines indicate that the blood lead levels in the lead based industrial workers could be accepted at this level as normal. An interesting observation is on the increased onset of osteoporosis in the urban population due to early exposure to lead as lead is known to interfere with

the calcium metabolism at all levels. Lead in bone has a half life of around 30 years and will be the constant supplier of endogenous lead. Even the calcium supplement provided to the osteoporosis patients is found to have unacceptable levels of lead.

NUTRITIONAL MANAGEMENT OF LEAD POISONING

Nutritional management of lead poisoning and prevention is of utmost importance all over the world today as very low levels of lead in the environment is found to effect undernourished population in both developed and developing countries. Use of vitamins and antioxidants in the diet seems to be of greater stress and economic feasibility when compared to the variety of expensive chelation treatment having many side effects (36-45). Man will continue to use lead in increasing amounts all over the world however, with better understanding at the level of nutritional requirement, essential metals and toxic heavy metal interaction, environmental management and National and International policies are expected to minimize the ill effects of lead (Table 1). In many recent studies role of essential trace minerals in the absorption of heavy metal lead is considered as an important factor, during the growth and development of a child.

Adequate supply of micronutrients in the diet is known to minimize the absorption of lead. Amongst them calcium, iron and zinc seems to have the maximal effects in lowering the ill effects of lead. Calcium deficiency and anemia increases blood lead levels. Ingested lead over a period of time results in anemia which further enhances the absorption of lead resulting in a vicious cycle. Hence the susceptibility to lead toxicity is more pronounced in developing countries due to poor nutritional status.

Nutritional deficiencies of essential metals can increase the hazard from lead exposure by enhancing absorption and toxicity of dietary lead. The essential metals with the most marked influence on blood lead levels and toxic effects are dietary levels of calcium, iron and zinc. Lead and calcium interactions are probably the most studied nutritional factors affecting lead toxicity (Table 2). There are several suggestions in the lead toxicity literature that the two metals are metabolically related. A study conducted by Aub and colleagues have shown that lead stream follows the calcium stream. A diet low in calcium containing varying levels of lead fed to rats, has resulted in considerably higher blood

and tissue levels of lead than those that occurred in rats fed a normal calcium diet. There are reports of many other experimental studies showing that absorption of lead by the gastrointestinal tract is inversely related to calcium content of the diet. Nutritional deficiency of calcium not only elevates blood lead levels, it also increases lead in the critical organ for toxicity in infants and young children. The Centre for Disease Control guidelines for prevention of childhood lead poisoning recommends adequate dietary calcium and iron as measures to prevent lead toxicity

Iron deficiency has been shown in experimental animals to increase lead absorption from the intestinal tract. Studies have found a negative correlation between blood lead and the ratio of iron-to-iron binding capacity for children between ages 9 and 11 years of age.

It has been shown experimentally that lead increases zinc excretion and that zinc deficiency enhances lead absorption. There is close inverse relationship between blood lead and activity of zinc-containing haem enzymes, particularly delta-aminolevulinic acid dehydratase, which suggests that lead replaces zinc in these enzymes

CHELATION TREATMENT

Chelation is the formation of a metal ion complex in which the metal ion is associated with a charged or uncharged electron donor referred to as ligand. An ideal chelator should have high solubility in water, resistance to biotransformation, ability to reach site of metal storage, ability to retain chelating ability at the pH of body fluid and property of forming metal complexes that are less toxic than the free metal ion. All chelating agents should be given to the patients who reside in environments free of lead during and after treatment. Several drugs are used in the treatment of lead poisoning. These drugs, capable of binding or chelating lead, deplete the soft and hard tissue lead, thus reducing its acute toxicity. All drugs have potential side effects and hence to be used with caution.

Following are some of the common chelating agents used for treatment of lead poisoning.

BAL (BRITISH ANTI-LEWISITE)

It is the first chelating agent specially developed to remove heavy metals from the body. It is very effective in treating heavy metal poisoning but it is

painful to administer because it requires intramuscular injection. It remains in use only because the more popular treatment CaNa_2EDTA requires its support in cases of severe lead poisoning (46).

CaNa_2EDTA (CALCIUM DISODIUM ETHYLENE DIAMINE TETRAACETIC ACID)

This is mainly used in treating childhood lead poisoning. It is used either as intramuscular or intravenous injections. The disadvantage in this drug is that it causes redistribution of lead from soft tissues to the central nervous system. EDTA removes lead only from the extra cellular compartment, because it does not enter cells. The weakness of this drug is that it does not chelate lead from the brain and it removes essential minerals such as zinc and calcium(47).

DMSA (2, 3 DIMERCAPTOSUCCINIC ACID)

The first oral chelator approved in the United States in 1991. DMSA is approved for children with blood lead levels greater than $45\mu\text{g/dl}$. DMSA is safe and target most heavy metals (mercury, arsenic, cadmium) and does not remove essential minerals.

It removes lead from the brain and does not redistribute lead to other organs following its therapy. It is water soluble and absorbed from the intestine(48,49).

DMPS (2,3 DIMERCAPTOPROPANE-1-SULPHONATE)

Like DMSA this is also relatively new, water soluble chelating agent. It is used more effectively in treating mercury poisoning than lead(50).

ROLE OF NATIONAL REFERRAL CENTER FOR LEAD POISONING IN INDIA

Raising public awareness about the dangers of lead poisoning from occupational and environmental sources is a crying need in Indian cities today. Since the problem of lead poisoning in India still exist and is raising, continuous efforts are needed to deal with the problem. A developing country like India can tackle this preventable environmental health hazard only through proper countrywide awareness, communication and education(ACE). In this regard National Referral Centre for Lead Poisoning was established in our Department of Biochemistry on August 6th 2001.

Table 1
Toxic-essential metal interactions

Toxic metal	Essential metal	Health effect
Cadmium	Zinc	Nephrotoxicity
	Iron	
Lead	Calcium	Cognitive/Behavioral effects in children
	Iron	
	Zinc	
Mercury	Selenium	CNS Toxicity
Aluminium	Iron	CNS Toxicity
	Calcium	Osteodystrophy
	Magnesium	
	Manganese	

Table 2

Lead effects on cellular calcium metabolism

1. Interferes with neurotransmitter kinetics
2. Blocks voltage-dependent calcium membrane channels
3. Substitutes for calcium in calcium-sodium pump
4. Competes for uptake by mitochondria
5. Binds to second messenger calcium receptors. Eg., calmodulin, protein kinase C

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