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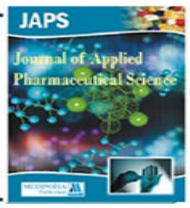

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The Efficacy and Undesired Effects of High Dosage Zinc Treatment

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ABSTRACT

Zinc is an essential micronutrient for human health. It is very important for body functions, and they have an interaction potential in several systems, including nervous system. Although there is no global regulation about the daily amounts, it is shown to reduce the incidence of diarrhea and pneumonia. Zinc deficiency is a global problem, especially in developing countries. Zinc has been shown to be effective in treatment of zinc deficiency, Acrodermatitis Enteropathica, protein energy malnutrition (PEM), Wilson disease, pica, diarrhea, unrecovering ulcers etc. Although under 50 mg daily is enough for diarrhea, anemia, infections, immundeficieny etc., higher dosages may be required in Wilson`s disease, pica and acrodermatitis enteropathica up to 220 mg daily. Also it was reported that high dosage of zinc treatment can lead neurotoxity, Alzheimer`s disease or impaired lipid metabolism. So caution should be exercised when prescribing the zinc to the patients who have risk for neurotoxity, Alzheimer`s disease or impaired lipid metabolism.

Keywords: Zinc Treatment, micronutrient, Zinc deficiency.

INTRODUCTION

Zinc is found in food generally in an organic form (in aspartate or gluconate) and this is the most absorbable form (Arcasoy and Cavdar, 1975). Zinc is an essential micronutrient for human health. It is very important for body functions, and they have an interaction potential in several systems, including nervous system. Although there is no global regulation about the daily amounts, it is shown to reduce the incidence of diarrhea and pneumonia. Zinc deficiency is a global problem, especially in developing countries. Zinc has been shown to be effective in treatment of zinc deficiency, Acrodermatitis Enteropathica, protein energy malnutrition (PEM), Wilson disease, pica, diarrhea, unrecovering ulcers etc. (Table 1).

Table. 1: Indications of zinc supplement.

Indications of Zinc Supplement
Zinc deficiency
Acrodermatitis Enteropathica
Protein energy malnutrition (PEM)
Wilson disease
Pica
Diarrhoea
Anemia
Thalassemia
Sickle Cell Anemia
Immundeficiency
Infections
Dermatological disorders
Growth retardation

Although under 50 mg daily is enough for diarrhea, anemia, infections, immundeficieny etc., higher dosages may be required in Wilson`s disease, pica and acrodermatitis enteropathica up to 220 mg daily.

THE EFFICACY OF HIGH DOSAGE ZINC TREATMENT

Acrodermatitis enteropathica

Acrodermatitis enteropathica (AE) is a rare autosomal recessive disorder of zinc deficiency (Maverakis et al, 2007). It is characterized by acral and periorificial dermatitis, alopecia, and diarrhea. Symptoms usually begin on weaning or formula feeding. In most of the few cases reported surviving to adult age, diarrhea is conspicuously absent. (Graves et al, 1989) It is characteristic for the disease to follow a fluctuating course with periods of remission. Individuals with AE suffer from severe zinc deficiency derived from a defective uptake of zinc in the duodenum and jejunum. The genetic defect has been mapped to 8q24 and the defective gene identified as SLC39A4, which encodes the zinc transporter Zip4. The diagnosis is made by way of clinical presentation together with histopathology and laboratory tests. Symptoms other than dermatitis, vary with age. Diarrhea, mood changes, anorexia, and neurological disturbance were reported most frequently in infancy. Growth retardation, alopecia, weight loss and recurrent infections were prevalent in toddlers and schoolchildren. The severity of symptoms also varies. Intermittent or mild cases of the disease and those presenting with uncommon features such as ophthalmic, cerebral or hepatic involvement, are easily overlooked. In the severe cases this may result in a fatal outcome. If untreated, the overall mortality rate is 20%, being higher in males. (Van Wouwe, 1989) Severe zinc deficiency as seen in acrodermatitis enteropathica is fatal, if zinc is not administered to these patients. (Prasad, 1995). An 11 year old patient with acrodermatitis enteropathica was given zinc sulphate 220 mg twice daily. At 6 weeks sore areas developed where plastic pants gripped the waist and thighs, and at 6 months thumb sucking caused saliva to induce lesions around the thumb and wrist. At 2 years old he developed hair loss and became bald. Between the ages of 2 and 5 years, photophobia developed to such an extent that schooling became difficult, yet ophthalmological examination revealed no abnormality. At the age of 11, a relapse was associated with profound hair loss and alopecia. Treatment with zinc sulphate 220 mg twice daily was initiated, and within two months the patient's skin, hair and eyes returned to normal. (Mortimer et al, 1984). In another case report the life course of acrodermatitis enteropathica was recorded in a 62-year-old white man. (Shelley, 1982) Initially saved in infancy by breast-feeding and good medical care, later in his twenties he responded well to diiodohydroxyquinoline therapy, his only residue being dermatitis, hoarseness, and short stature. Subsequently, oral zinc therapy initiated for the first time cleared his acrodermatitis, which had been present for 60 years. Acrodermatitis enteropathica may be viewed as having a malignant potential over the long term. The zinc-dependent nature of the immune deficit, however, suggests that lifelong daily zinc supplementation is an appropriate prophylactic measure. In the light of published data it is possible to say that oral administration of zinc sulfate, 5 to 10 mg/kg daily, rapidly reverses the cutaneous lesions. Improvement is noted within days and clearance occurs within 2 to 3 weeks. Stool patterns quickly return to normal after treatment. It was reported that signs and symptoms of the acrodermatitis enteropathica like syndrome may occur as a secondary disease to alcoholism (Chauldry et al, 2008. West, Anderson, 1986), parenteral nutrition (Löffler and Effendy, 1999. Strobel et al, 1978) and Crohn disease (Krasovec and Frenk, 1996. Kaufmann, 1984) in adults. So, it could be said that patients may need zinc supplement in their whole life.

Wilson disease

Wilson disease is a rare disorder of copper metabolism that results in accumulation of copper in the liver and other tissues; mostly the central nervous system and the kidneys. Zinc was introduced in the management of Wilson disease in the early 1960s. Since then a significant number of studies on its usage have been published. Zinc is presumed to induce metallothionein in the intestine and the liver, thereby sequestering it. Studies are unable to address zinc monotherapy as an effective “decoppering” agent, since most patients had received other chelating agents. Zinc therapy is efficacious in presymptomatic patients. Zinc can be used in conjunction with another chelating agent or alone when intolerance develops to both penicillamine and trientine. (El-Youssef, 2003). Data on zinc in the treatment of Wilson disease have been derived from uncontrolled studies using different zinc preparations (zinc sulphate, zinc acetate) at different doses (75–250 mg/day). The efficacy of zinc has been assessed by different approaches. First, patients successfully decoppered by d-penicillamine were switched to zinc and the maintenance of their asymptomatic condition was monitored. Second, symptomatic patients switched to zinc as an alternative treatment due to intolerance to d-penicillamine. Third, zinc was used as first-line therapy. All treatment alternatives were effective. In the light of these approaches it could be said that zinc was better tolerated than d-penicillamine. (Ferenci, 1998). A retrospective cohort analysis was performed on Wilson disease (Merle et al, 2006). Patients were treated with zinc salts (150–250 mg/day). Long-term observation was reflected in a mean follow-up of 16.7 years. It was reported that zinc treatments were effective. Zinc is an effective maintenance treatment in Wilson diseases and has no or minimal

side effects. Therefore zinc is an essential component of treatment in the vast majority of patients. (Taly et al, 2009).

Pica

Pica is a medical disorder characterized by an appetite for substances largely non-nutritive (e.g. metal (coins, etc), clay, coal, soil, feces, chalk, paper, soap, mucus, ash, gum, etc.) or an abnormal appetite for some things that may be considered foods, such as food ingredients (e.g., flour, raw potato, raw rice, starch, ice cubes, salt). Pica is seen in all ages, particularly in pregnant women, small children, and those with developmental disabilities. A research on the causes of pica suggests that the disorder is caused by mineral deficiency in many cases, typically iron and zinc deficiency. An observational trial was performed by Singhi and colleagues. It was reported that plasma Zn levels in the pica group (60 +/- 4.4 mg/dl) was about 45% lower than those in controls (110.2 +/- 8.5 mg/dl, $p<0.001$) and suggested that hypozincemia with low iron levels may be the possible cause of pica. Therefore, low levels of plasma Zn and Fe could be an effect of pica. (Singhi et al, 2003) So zinc supplementation could be effective in pica.

The Undesired Effects of Zinc

Zinc is a nutrient metal that in high dosage can paradoxically promote oxidative toxicity. There is evidence of neurotoxicity when it is found in excess in the brain. Excess zinc is a common finding in neurodegenerative disease and is involved in the neuronal injury observed in cerebral ischemia, epilepsy, and brain trauma. Toxic zinc accumulation may result from either transsynaptic Zn movement or mobilization from intracellular sites, such as Zn flux through receptor associated calcium channels, voltage-sensitive calcium channels, or Zn-sensitive membrane transporters. The mechanisms by which Zn exerts its neurotoxicity include mitochondrial production of reactive oxygen species and the disruption of metabolic enzymes, ultimately leading to activation of apoptotic processes. It was reported that an exciting new area of research is the role of Zn metabolism in Alzheimer's disease as a trigger for amyloid-b aggregation and neuronal plaque formation as with Cu, Fe, and Mn (Wright and Baccarelli, 2007). Also Zn^{+2} is being associated with beta-amyloid aggregation which is believed to induce neurotoxic effects (Bush and Tanzi, 2008). On the other hand zinc can effect the lipid metabolism. HDL levels tend to decrease especially after 50 mg daily prescriptions, while total cholesterol, LDL-c and triglyceride levels tend to be stabile up to zinc treatments 150 mg daily. Also, data suggest that sustained hyperzincaemia predisposes individuals to thrombogenesis, whereas acute zinc depletion impairs platelet aggregation and prolongs bleeding time. Supplementation with 50 mg zinc daily, resulting in a postprandial rise in the plasma zinc concentration, increased platelet reactivity (Hughes and Samman, 2006).

CONCLUSION

Zinc has been shown to be effective in treatment of zinc deficiency, Acrodermatitis Enteropathica, protein energy malnutrition (PEM), Wilson disease, pica, diarrhea, unrecovering ulcers etc. Although under 50 mg daily is enough for diarrhea, anemia, infections, immundeficieny etc., higher dosages may be required in Wilson`s disease, pica and acrodermatitis enteropathica up to 220 mg daily. Also it was reported that high dosage of zinc treatment can lead neurotoxity, Alzheimer`s disease or impaired lipid metabolism. So caution should be exercised when prescribing the zinc to the patients who have risk for neurotoxity, Alzheimer`s disease or impaired lipid metabolism. Therefore high dosage zinc should only prescribe to patients who really need high dosage zinc treatment like Wilson`s disease, pica and acrodermatitis enteropathica. Further analysis is needed to investigate the effects of high dosage zinc treatment.

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