Bull. Environ. Contam. Toxicol. (1996) 56:178-182
© 1996 Springer-Verlag New York Inc.

Bulletin of Environmental Contamination and Toxicology

Levels of Cerium in the Tissues of Rats Fed a Magnesium-Restricted and Cerium-Adulterated Diet

J. T. Eapen, C. C. Kartha, K. Rathinam, M. S. Valiathan

Division of Cellular and Molecular Cardiology and *Division of Materials Toxicology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum 695 011, India

Received: 13 March 1995/Accepted: 20 July 1995

Cerium, a lanthanide, is the most abundant rare earth element present in monazite and is biologically active. It has been postulated that cerium toxicity in conjunction with magnesium deficiency causes tropical endomyocardial fibrosis, a restrictive human cardiomyopathy (Valiathan et al. 1989; Valiathan and Kartha 1990). Generally, lanthanides are known to be poorly absorbed (Durbin et al. 1956; Evans 1990). The present study was carried out to ascertain whether magnesium deficiency promotes accumulation of cerium in various organs of rats.

MATERIALS AND METHODS. Magnesium-deficient and magnesium sufficient diets were purchased from Zeigler Bros, USA. Magnesium-sufficient and deficient diets contained 0.515% and 0.008% of magnesium, respectively (Anonymous 1977). A magnesium-restricted diet was prepared in the laboratory by adding the required amount of magnesium sulphate to powdered magnesium-deficient diet. This diet contained 0.012% of magnesium. Diets containing cerium were prepared by adding cerium sulphate [$Ce(SO_4)_2.4H_2O$] (E-Merck, Germany) to provide a concentration of 35 ppm. Ce levels in the diet were determined and the homogeneity was confirmed in the re-pelleted diet. The diets were fed ad libitum.

Thirty six, one month old CFY/NIN albino rats (initial weight 58.1 ± 3.4g; male:female = 1:l) were randomly distributed into four experimental groups (A,B,C & D) following a 2 x 2 factorial design.

Animals in two groups (A & B) were given a magnesium-sufficient diet containing 0.515% magnesium while animals in other two groups (C & D) were given the magnesium-deficient diet containing 0.008% of magnesium. After a month, in order to prevent mortality due to acute magnesium deficiency, the diet of animals

Correspondence to: J. T. Eapen

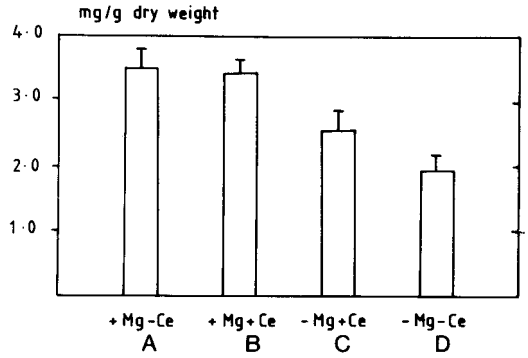

Figure 1. Magnesium levels in bone from rats of different experimental groups.

in group C & D was substituted with Mg restricted diet containing 0.12% of magnesium. This level was derived on the basis of earlier studies where viability could be maintained by giving a minimal amount of magnesium. The diets of rats in groups B and D also contained cerium (35 ppm).

The animals were monitored during the experimental period. Their body weight as well as food and water intake were regularly recorded. Symptoms of toxicity, if any, were also recorded. Dead animals were autopsied. After 3 months, before the termination of the experiment, the rats were weighed. Animals in all the 4 groups were sacrificed, their heart, lung, kidney, skeletal muscle, liver and bone (femur) were removed, weighed and dried.

A part of the tissue was digested with concentrated HNO_3 and $HClO_4$ and magnesium was determined by atomic absorption spectometry (International Laboratory IL 551, USA). The remaining part of the dried tissue was used for determining its cerium content. Cerium analysis was carried out by neutron activation analysis. Details of both the analyses in tissues and diets are described elsewhere (Valiathan et al. 1989; Valiathan et al. 1986).

The results were evaluated by analysis of variance (ANOVA) using computer programmed MINITAB release 5.1 (SPSS Inc., USA)). To compare between the two groups, the Mann-Whitney U-test was employed. The results were considered significant when p was <0.05.

RESULTS AND DISCUSSION. The animals fed a magnesium-deficient diet (Groups C and D) developed classical

signs of magnesium deficiency after two weeks. They had alopecia, yellowish discolouration of skin and a peculiar unpleasant odour. After one month on the magnesium-restricted diet, these symptoms of magnesium deficiency disappeared. There was no significant difference in the body weight or the heart:body weight ratio of rats from the four groups.

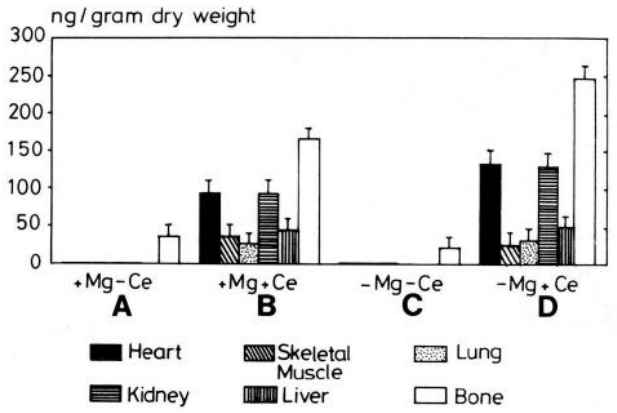

Figure 2. Cerium levels in various tissues from rats of different experimental groups.

Figure 1 shows the levels of magnesium in the bone of the animals. A significant decrease in magnesium levels in the bone was observed in animals fed the magnesium-deficient diet. No significant difference in Mg levels was observed in the tissues in animals from the 4 groups.

Figure 2 shows cerium levels in different tissues. Cerium accumulated in all the tissues of animals in Groups B and D. Bone accumulated maximum cerium. In group D, levels of cerium in the bone, kidney and heart were significantly higher as compared to Group B.

There is increasing interest in the toxicology of cerium since the element is widely used in modern industry as in petrochemicals, metallurgy, television and optics (Evans 1990). Pneumoconiosis is an occupational hazard resulting from inhalation of air containing cerium particles (Vocatura et al. 1983). Recently, we have reported the presence of cerium in the heart tissue of patients with endomyocardial fibrosis, a restrictive human cardiomyopathy prevalent in the tropics. Based on elemental analysis of the diseased cardiac tissue, it was hypothesised that endomyocardial fibrosis is possibly the cardiac expression of a synergestic effect of magnesium deficiency and cerium toxicity (Valiathan and Kartha

1990). Studies conducted out in this laboratory raised the possibility that cerium mimic the functional effect of magnesium (Shivakumar et al. 1989). Further, very low levels of cerium (100 nM) have been shown to increase collagen synthesis in cardiac fibroblasts in vitro (Shivakumar et al. 1992). Interestingly, cerium toxicity to myocardial cells is enhanced by magnesium deficiency (Shivakumar and Nair 1991). The present experiment was to ascertain the role of magnesium deficiency in the accumulation of cerium in the tissues.

Magnesium deficiency in rats was produced by feeding them a magnesium-restricted diet. The signs of magnesium deficiency observed in the rats were as described by earlier workers (Watchorn and McCance 1937; Kubena et al. 1988). In our earlier studies, it was observed that rats did not survive if acute magnesium deficiency persisted (unpublished observations). To overcome this difficulty, after feeding the rats a magnesium-deficient diet for a month, they were maintained on a magnesium-restricted diet during the rest of the experimental period. Though the external signs of magnesium deficieny were not noticeable following the change of diet, magnesium level in the bone shows that animals in Groups C & D had developed chronic magnesium deficiency. Magnesium levels in bone were significantly lower ($p<0.05$) in these groups as compared to the groups fed the magnesium-sufficient diet. Since bone is the primary repertoire of magnesium in the body (Aikawa 1981), it is sensitive to changes in availability and, during magnesium deficiency conditions, magnesium is mobilized from bone to maintain homeostasis.

The results showed that among the animal groups fed cerium-adulterated diets, the tissues level of cerium were significantly higher in magnesium-deficient group than in the magnesium-sufficient group (Fig 2). Gastro-intestinal absorption of cerium is shown to be poor in all mammalian species studied (Durbin et al. 1956; Evans 1990). However, it is reported that absorption of cerium is greater in younger animals and in dietary deficiencies of calcium, phosphorus and vitamin A (Venugopal and Luckey 1978).The mechanism by which magnesium deficiency may promote accumulation of cerium in the tissues is not clear. However, magnesium deficiency has been shown to enhance membrane permeability (Gunther 1990), which may result in increased uptake by absorptive surfaces of the gut. Moreover, magnesium deficiency is known to cause histologic lesions in kidneys (Seelig 1980) which can impair excretion of cerium from the body.

Acknowledgments. Supported by a grant from Indian

Council of Medical Research. The authors thank Dr. C.M. Sunta and Dr. R.C. Sharma Internal Dosimetry Section, Bhabha Atomic Research Centre, Bombay for extending facilities for neutron activation analysis.

REFERENCES

Aikawa JK (1981) Magnesium: Its biologic significance. CRC Press, Florida

Anonymous (1977) American Institute of Nutrition adhoc committee on standards for nutritional studies. J Nutrition 107:1340-1348

Durbin PW, Williams MH, Gee M, Newman RH, Hamilton JG (1956) Metabolism of lanthanons in rat. Proc Soc Exp Biol Med 91:78-85

Evans CH (1990) Biochemistry of lanthanides. Plenum Press, New York

Gunther T (1990) Magnesium deficiency generally enhances cytotoxicity. Magnesium Bull 12:61-64

Kubena KS, Edgar SE, Veltmann JR (1988) Growth and development in rats and deficiency of magnesium and pyridoxine. J Am Coll Nutr 7:317-324

Seelig MS (1980) Magnesium deficiency in the pathogenesis of disease. Early roots of cardiovascular, skeletal, and renal abnormalities. Plenum Medical Book Co, London

Shivakumar K, Appukuttan PS, Kartha CC (1989) Interactions of thorium and cerium with adenine nucleotides. Biochem Int 19:845-853

Shivakumar K, Nair RR (1991) Cerium depresses protein synthesis in cultured cardiac myocytes and lung fibroblasts. Mol Cell Biochem 100:91-96

Shivakumar K, Nair RR, Valiathan MS (1992) Paradoxical effect of cerium in collagen synthesis in cardiac fibroblasts. J Mol Cell Cardiol 24:775-780

Valiathan MS, Kartha CC, Panday VK, Dang HS, Sunta CM (1986) A geochemical basis for endomyocardial fibrosis. Cardiovasc Res 20:679-682

Valiathan MS, Kartha CC, Eapen JT, Dang HS, Sunta CM (1989) A geochemical basis for endomyocardial fibrosis. Cardiovasc Res 23:647-648

Valiathan MS, Kartha CC (1990) Endomyocardial fibrosis - the possible connection with myocardial levels of magnesium and cerium. Int J Cardiol 28:1-5

Venugopal B, Luckey TD (1978) Metal toxicity in mammals. Plenum Press, New York

Vocatura, G, Colombo F, Zanoni M, Rodi F, Sabbioni E, Pietra R (1983) Human exposure to heavy metals; rare earth pneumoconiosis in occupational workers. Chest 83:780-783

Watchorn E, McCance RA (1937) Subacute magnesium deficiency in rats. Biochem J 31:1379-1390