Magnesium

Introduction

Magnesium plays a vital role in a wide range of biochemical and physiological processes, particularly those involving energy metabolism and utilization as well as bone structure (Institute of Medicine [IOM] 1997; Shils 1999). Clinical consequences of magnesium deficiency include a variety of neurological and neuromuscular signs such as tremors, spasms, and altered reflexes. In addition, magnesium deficiency may cause or exacerbate myocardial infarction, arrhythmia, and associated mortality. It is often brought on not only by dietary inadequacy but also by malabsorption; kidney dysfunction, often as increased excretion under the influence of diuretic drugs (National Institutes of Health [NIH] 2013); endocrine disorders; genetic and congenital disorders; and alcoholism (Shils 1996; NIH 2013). Magnesium is efficiently absorbed in the intestine, and body concentrations are controlled primarily through the regulation of urinary excretion rates. It is stored and reserved in the skeleton (Shils 1994, 1999; IOM 1997).

Safety Considerations

Healthy human kidneys are capable of rapidly excreting large amounts of absorbed or injected magnesium. Even after large intakes, serum levels usually stay within the usual and safe range (IOM 1997; Shils 1999). Subjects with normal kidneys can excrete 40 to 60 g of magnesium per day without side effects when the mineral is administered via persistent infusion. Elevated serum levels may occur when drugs that contain magnesium, usually antacids and cathartics, are taken in excess of 15 g per day on a chronic basis (Smilkstein et al. 1988). Moderate increases in plasma magnesium levels may induce symptoms such as nausea, vomiting, and hypotension (Shils 1996, 1999; NIH 2013). Due to the major involvement of magnesium in neurological functions, the elevated plasma levels that occur as a result of large intravenous infusions can cause adverse effects to become more severe and sometimes life-threatening.

Adverse effects of magnesium are primarily related to three conditions: neonatal neural depression after intravenous maternal treatment for eclampsia, accidental or deliberate poisoning

with very large single doses, and increased sensitivity to magnesium-containing drugs in people with renal failure (Flink 1976). Aside from osmotic diarrhea related to unabsorbed magnesium, there is no evidence that large quantities of oral magnesium are harmful to people with normal kidney function (IOM 1997).

Average total dietary intakes of magnesium by U.S. adults is 300 to 400 mg per day (IOM 1997; Hunt and Johnson 2006). Supplemental intakes of 375 mg lack any known adverse effects (Stendig-Lindberg et al. 1993), and it is not until supplements reach levels greater than 10 mg per kg per day (700 mg in a 70-kg person) that plasma magnesium concentrations become elevated (Durlach et al. 1994).

Possible negative consequences of calcium's interaction with magnesium have been hypothesized but have not been reported.

Official Reviews

IOM (1997). The IOM concluded that the magnesium found in foods has not been found to produce adverse effects and that "the primary initial manifestation of excessive magnesium intake from other oral nonfood sources is diarrhea." The physiological effects of longer-term high intakes of oral magnesium have been observed only in persons with abnormal kidney function. Thus, the critical adverse effect identified as the appropriate basis for the magnesium UL is diarrhea. In its dose-response evaluation, the IOM identified a few studies, mainly in the frail elderly, that found some increase in the incidence of diarrhea with supplemental intakes of magnesium chloride or other soluble salts in the range of 360 to 460 mg of magnesium per day (Marken et al. 1989; Ricci et al. 1991; Bashir et al. 1993), but noted that foods enriched with 452 mg of magnesium as magnesium oxide did not cause diarrhea (Altura et al. 1994). Another study (Stendig-Lindberg et al. 1993) found no diarrhea in postmenopausal women who were given up to 678 mg magnesium as magnesium hydroxide. Similarly, diabetic subjects supplemented with 400 mg magnesium as an oxide or chloride experienced no diarrhea (Nadler et al. 1992). Elderly subjects given 372 mg of magnesium did not have any increase in diarrhea or gastrointestinal complaints (Paolisso et al. 1992). On the basis of these studies, in particular that of Bashir and

coworkers, the IOM identified a LOAEL of 360 mg for nonfood magnesium. To derive the UL, the IOM selected a UF of 1.0, even though it was being applied to a LOAEL, because of "the very mild, reversible nature of osmotic diarrhea caused by ingestion of magnesium salts." The relative adverse effects of the different chemical compounds of magnesium have not been systemically studied.

European Commission, Scientific Committee on Food (EC SCF 2001). The EC SCF agreed that osmotic diarrhea is the critical effect for identification of a UL for magnesium. It identified a LOAEL of 360 mg and a NOAEL of 250 mg per day for nonfood magnesium. Selecting a UF of 1.0 for application to the 250 mg NOAEL, the SCF derived a UL of 250 mg per day.

Expert Group on Vitamins and Minerals (EVM 2003). The UK's EVM concurred that osmotic diarrhea is the adverse effect of concern, but determined that the data are insufficient to establish an SUL value. Instead, they established a guidance level of 400 mg per day for nonfood magnesium because "it would not be expected to result in any significant adverse effects."

All three reviews found no evidence that magnesium intake from food causes osmotic diarrhea but that nonfood sources such as supplements, laxatives, and antacids have the potential to produce these mild, reversible adverse effects. Thus, the SUL or guidance values identified were applied to nonfood sources only.

CRN Recommendations

The only severe adverse effects reliably attributed to oral consumption of magnesium relate to prolonged use in multiple-gram quantities as an antacid or cathartic. Mild to moderate but infrequent and easily reversible diarrhea can result from nonfood magnesium intakes at levels above 400 mg per day. The mild nature of this adverse effect makes a LOAEL unnecessary and suggests that a UF of 1.0 is appropriate for deriving a UL for supplements. Thus, the CRN UL for supplemental magnesium is 400 mg per day for healthy adults. Multiple doses separated by several hours is preferred in order to further dilute any adverse effects. Individuals consuming supplements should be aware that some antacids and laxatives also contain magnesium.

Quantitative Summary for Magnesium

CRN UL, supplemental intake	400 mg/day
IOM UL, nonfood sources	350 mg/day
EC SCF UL, nonfood sources	250 mg/day
EC supplement maximum	Not determined
EVM, guidance level, supplemental intake	400 mg/day

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