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Nutritional aspects of manganese homeostasis

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Abstract

Manganese (Mn) is an essential mineral. It is present in virtually all diets at low concentrations. The principal route of intake for Mn is via food consumption, but in occupational cohorts, inhalation exposure may also occur (this subject will not be dealt with in this review). Humans maintain stable tissue levels of Mn. This is achieved via tight homeostatic control of both absorption and excretion. Nevertheless, it is well established that exposure to high oral, parenteral or ambient air concentrations of Mn can result in elevations in tissue Mn levels. Excessive Mn accumulation in the central nervous system (CNS) is an established clinical entity, referred to as manganism. It resembles idiopathic Parkinson's disease (IPD) in its clinical features, resulting in adverse neurological effects both in laboratory animals and humans. This review focuses on an area that to date has received little consideration, namely the potential exposure of parenterally fed neonates to exceedingly high Mn concentrations in parenteral nutrition solutions, potentially increasing their risk for Mn-induced adverse health sequelae. The review will consider (1) the essentiality of Mn; (2) the concentration ranges, means and variation of Mn in various foods and infant formulas; (3) the absorption, distribution, and elimination of Mn after oral exposure and (4) the factors that raise a theoretical concern that neonates receiving total parenteral nutrition (TPN) are exposed to excessive dietary Mn.

Keywords

Manganese; Total parenteral nutrition; Formula; Central nervous system

1. The essentiality of manganese

Manganese (Mn) is an essential trace metal that is found in all tissues and is required for normal amino acid, lipid, protein, and carbohydrate metabolism. Mn-dependent enzyme families include oxidoreductases, transferases, hydrolases, lyases, isomerases, and ligases. Manganese metalloenzymes include arginase, glutamine synthetase, phosphoenolpyruvate decarboxylase, and Mn superoxide dismutase (Mn SOD). Mn is involved in the function of numerous organ systems. It is needed for normal immune function, regulation of blood sugar

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and cellular energy, reproduction, digestion, bone growth, and it aids in defense mechanisms against free radicals. Mn in concert with vitamin K supports blood clotting and hemostasis.

No formal recommended dietary allowance (RDA) for Mn has been established, but the US National Research Council (NRC) has established an estimated safe and adequate dietary intake (ESADDI) of 2–5 mg/day for adults (Greger, 1998). Factors that influence the daily Mn requirement have been recently reviewed (National Academy of Sciences, 2001), and some of these factors will be detailed below in Section 2. The National Academy of Sciences (2001) has established an adequate intake (AI) for Mn. AI is defined as a nutrient consumption value that is experimentally derived or is an approximation of an observed mean nutrient intake for a group of apparently healthy individuals. An AI is established when there is not sufficient scientific evidence to calculate an estimated average requirement (EAR). The EAR is the daily intake value that is estimated to meet the nutritional requirement, as defined by a specific indicator of adequacy, in one-half of the apparently healthy individuals in a life stage or gender group. The AI replaces the ESADDI. The Mn AI for adult men and women is 2.3 and 1.8 mg/day, respectively (National Academy of Sciences, 2001). Lactation and gestation increase the Mn requirement (National Academy of Sciences, 2001). Developmental life stage can also influence dietary Mn requirements. Adequate intakes for newborn (<6 months of age) infants are approximately 3 µg/day while intakes increase to 600 µg/day by 7–12 months of age (National Academy of Sciences, 2001). Children between 1–3 and 4–8 years of age have adequate daily Mn intakes of approximately 1.2 and 1.5 mg/day, respectively.

Though not frequently encountered, inadequate dietary intake and Mn deficiency lead to impaired growth, poor bone formation and skeletal defects, reduced fertility and birth defects, abnormal glucose tolerance, and altered lipid and carbohydrate metabolism (Freeland-Graves and Llanes, 1994; Keen et al., 1999). Men experimentally placed on Mn-depleted diets developed an erythematous rash on their torsos (Friedman et al., 1987), and women consuming <1 mg Mn/day in their diet developed altered mood and increased pain during the premenstrual phase of their estrous cycle (Penland and Johnson, 1993). Interestingly, non-experimentally induced Mn deficiency in humans has not been reported.

While naturally occurring deficiency states have not been recognized, Mn-induced neurotoxicity from excess respiratory or dietary exposures has been well described. Though not within the scope of this review, there are numerous theories regarding potential mechanisms of Mn-induced neurotoxicity. For extensive review please refer to Fitsanakis et al. (2004). Oxidative stress is one of many factors implicated in Mn-induced neurotoxicity (Aschner, 1997). Dopamine oxidation by Mn is a potential mechanism for Mn-induced oxidative stress, especially since Mn preferentially accumulates in dopamine-rich brain regions (e.g., basal ganglia) (Sloot et al., 1996). It has also been suggested given its sequestration by mitochondria, Mn interferes with proper respiration, thereby leading to excessive production of reactive oxygen species (ROS). Inhibition of complex I of the electron transport chain as well as the ATPase complex by Mn has also been noted (Gavin et al., 1999). Mn in the 3+ oxidation state is more effective at inhibiting complex I (Archibald and Tyree, 1987), but the divalent form is by far the predominant species within cells and is largely bound to ATP. Nevertheless, in biological media, Mn in any oxidation state may

spontaneously give rise to infinitesimal amounts of Mn 3+, which even at trace amounts can lead to ROS formation, lipid peroxidation and ensuing cell death (HaMai et al., 2001).

2. The concentration ranges, means and variation of manganese in various foods and infant formulas

Diet represents the major source of human Mn intake. In the general population, enteral intake of this essential metal is <5 mg Mn/kg (with a range of 0.9–10 mg Mn/day; Agency for Toxic Substances and Drug Registry, 2000). Major sources of dietary Mn include grain, rice, and nuts (~30 mg Mn/kg). Another source rich in Mn content is tea (with Mn levels of 0.4–1.3 mg/cup; Agency for Toxic Substances and Drug Registry, 2000). Dietary supplements are also fortified with Mn, and some contain levels as high 5–20 mg Mn (National Academy of Sciences, 2001). Mn concentrations in drinking water range from 1 to 100 µg/l, with most sources containing >10 µg/l (Keen and Zidenberg-Cherr, 1994).

Infant diets contain a wide range of Mn. As shown in Table 1, the content of Mn in human milk is 3–10 µg/l while that of soy formula is 100-fold higher at 200–300 µg/l (Lonnerdal, 1994). Cow's milk-based infant formulas are intermediate in their Mn content (Table 1). There is no evidence that the low Mn content of human milk results in Mn deficiency, nor is there any evidence that the higher Mn content of infant formulas is associated with toxicity. It has been shown that adults absorb 8% of the Mn from human milk, but only 2% from bovine milk, and <1% from soy formula (Davidsson et al., 1989). Data on the intestinal control of Mn absorption in human neonates are limited. However, Wilson et al. (1992) reported no significant differences in mean plasma Mn concentrations between preterm infants fed maternal milk containing 4.1 µg Mn/l or preterm infant formula containing 303 µg Mn/l. This wide safety margin implies that even preterm infants have effective homeostatic mechanisms that ensure little change in body Mn over a wide range of Mn intake. These homeostatic mechanisms are at the level of intestinal absorption and Mn excretion via the biliary tract (Hambidge et al., 1989).

3. The absorption, distribution, and elimination of oral manganese

Approximately 1–5% of ingested Mn is normally absorbed (Davis et al., 1993). In adults the net gastrointestinal absorption (mean ± SD) of radiolabeled ⁵⁴Mn from a meal containing 1 mg Mn is 1.35 ± 0.51 and 3.55 ± 2.11% for adult men and women, respectively (Finley et al., 1994). The mean (±SD) retention 10 days after ingestion of 0.3 mg Mn was estimated at 5.0 ± 3.1% in young adult women (Davidsson et al., 1988). Gender differences for Mn absorption have been noted, men absorbing significantly less Mn compared to women. It has been postulated that reduced gastrointestinal Mn absorption in men reflects the iron status and the higher serum ferritin concentrations in men (Finley et al., 1994; Finley, 1999; National Academy of Sciences, 2001).

Within the plasma, Mn is largely bound to gamma-globulin and albumin, and a small fraction of trivalent (3+) Mn is bound to the iron-carrying protein, transferrin (Aisen et al., 1969). Mn absorption by the gastrointestinal tract is influenced by several factors. For example, the concentration of Mn in the diet is known to influence the amount of Mn

absorbed from the gastrointestinal tract as well as its elimination via the bile. Adaptive changes to high dietary Mn intake include reduced gastrointestinal tract absorption, enhanced liver metabolism, and increased biliary and pancreatic excretion of this metal (Britton and Cotzias, 1966; Davis et al., 1993; Dorman et al., 2001, 2002; Finley and Davis, 1999; Malecki et al., 1996). Mn absorption from the diet is also influenced by the presence of other trace minerals, phytate, ascorbic acid, and other dietary constituents (Davidsson et al., 1991).

Competition between Mn and iron (Fe) at the gastrointestinal tract has been documented, and it is most likely mediated via the divalent metal transporter 1 (DMT-1) (Gunshin et al., 1997). Furthermore, absorption of Mn from the gastrointestinal tract is also influenced by the age of an individual. Absorption of Mn is high during the neonatal period (Keen et al., 1986). Compared to adults, human infants also have higher retention of ingested Mn during the early neonatal period (Zlotkin et al., 1995; Dörner et al., 1989), with Mn retention in formula-fed term infants approximating 20% of oral intake. The developing rodent brain takes up approximately 8% of the total ingested oral Mn during the early neonatal period (Keen et al., 1986).

The “normal” range of mammalian tissue Mn concentrations is 0.3–2.9 µg Mn/g wet tissue weight (Keen and Zidenberg-Cherr, 1994; Rehnberg et al., 1982). Tissues with high energy demand (brain) and high pigment content (e.g., retina, dark skin) have the highest Mn concentrations. Typically, bone, liver, pancreas, and kidney also have high Mn concentrations.

⁵⁴Mn tracer techniques have been extensively used to determine whole-body elimination of Mn. Whole-body elimination of a single tracer dose of ⁵⁴Mn is biphasic (Britton and Cotzias, 1966; Mahoney and Small, 1968; Papavasiliou et al., 1996). Dose-dependent elimination of a trace dose of ⁵⁴Mn has been noted in miners (Cotzias et al., 1968).

Biliary secretion is the main pathway for Mn excretion (Davis et al., 1993; Malecki et al., 1996). Irrespective of the level of Mn intake, adult humans generally maintain stable tissue Mn concentrations, achieved by tightly controlled regulation of absorption and excretion rates. In the liver, Mn is removed from the blood, conjugated with bile and excreted into the intestine. A small fraction of Mn in the intestine is reabsorbed, establishing de facto an enterohepatic circulation (Schroeder et al., 1996). Biliary excretion is poorly developed in neonatal animals, and exposure during this period may result in increased delivery of Mn into the brain and other tissues. In mice, rats, and kittens, there is an almost complete absence of biliary Mn excretion during the neonatal period (Cotzias et al., 1976). Pancreatic excretion of Mn contributes only a small fraction of the absorbed Mn dose (Davis et al., 1993). Urinary excretion of Mn is generally low.

4. Factors that raise a theoretical concern that neonates receiving total parenteral nutrition (TPN) are exposed to excessive dietary manganese

It is very common for premature or critically ill infants to be nourished parenterally. Parenteral nutrition solutions contain variable quantities of Mn as a contaminant (Kurkus et

al., 1984; Hambidge et al., 1989; Wilson et al., 1992). Wilson et al. (1992) reported that the Mn content of TPN solutions in the *absence* of trace element supplementation was 7.3 µg/l (range 5.6–8.9 µg/l; Table 2).

It is standard clinical practice to supplement infants receiving parenteral nutrition with a neonatal trace element solution (Multitrace®–4 Neonatal; American Regent, Inc., Shirley, NY) containing 25 µg/ml Mn (Committee on Nutrition, 1985). While there is some practice variation among neonatal intensive care units, this supplement is most often added at a dose of 0.2 ml/kg or 0.2 ml/dl of parenteral nutrition solution. At the typical targeted fluid volume of 150 ml/kg/day of TPN, this will provide an additional 5.0–7.5 µg/kg of Mn (depending on whether the supplement is added based on the infant's weight in kilograms or based on the volume of TPN delivered; Table 2).

As noted earlier, approximately 8% of Mn in human milk is absorbed (Davidsson et al., 1989). By comparison, retention of intravenous Mn is close to 100%. Thus, the total Mn delivered in trace element-supplemented TPN is approximately 6–8.5 µg/kg/day, about 100 times the Mn burden of infants fed human milk (Table 2). Mn intoxication has been reported in association with TPN solutions providing 0.1 mg Mn/day, ~1.5–2.0 µg/kg/day for an average adult (Ono et al., 1995; Nagatomo et al., 1999; Bertinet et al., 2000; Takagi et al., 2002).

There are additional considerations that raise concern about excessive Mn delivery to the parenterally fed neonate. Not only is the absorptive control of the intestine bypassed in infants receiving Mn-supplemented TPN, but the excretion of Mn is likely to be minimal as parenterally fed infants pass little or no stool and frequently develop overt evidence of hepatic dysfunction and cholestasis. More than 90% of Mn is excreted through the bile (Malecki et al., 1996; Agency for Toxic Substances and Disease Registry, 2000). Hepatic dysfunction and cholestasis are known risk factors for increased accumulation of Mn in the brain in both humans and animal models (Ballatori et al., 1987; Krieger et al., 1995; Malecki et al., 1996; Montes et al., 2001; Erikson and Aschner, 2003). Patients with portosystemic shunts and biliary atresia display hypermanganesemia, even in the absence of increased dietary Mn (Rose et al., 1999; Reimund et al., 2000; Ikeda et al., 2000a,b). Autopsy studies in adult patients with chronic hepatic encephalopathy have revealed elevated Mn levels in the basal ganglia (Krieger et al., 1995).

Data in children are more limited than in adults. Barron et al. (1994) described an 8-year-old girl with Alagille syndrome and chronic hepatic failure who developed dystonia in association with elevated whole-blood Mn levels. Fell et al. (1996) described two children with cholestasis receiving parenteral nutrition for 8 and 16 months who displayed movement disorders and very high whole-blood Mn concentrations. Discontinuation of parenteral Mn supplements has been associated with a rapid decrease in plasma Mn levels and improved liver function (Hambidge et al., 1989). Notably, it is recommended that Mn supplements be withheld from adults and children with cholestasis receiving TPN.

In 1985, The American Academy of Pediatrics Committee on Nutrition recommended a Mn intake of 2–10 µg/kg/day for exclusively parenterally fed preterm infants. This became the

standard of care throughout the US, and has influenced the composition of commercial currently available multiple trace element products. However, recommendations for Mn supplementation in TPN for the pediatric and neonatal populations have recently been revised. The Pediatric Nutrition Handbook—5th Edition (2003) recommends 1 µg/kg/day. The new A.S.P.E.N. report (2004) also recommends 1 µg/kg/day for preterm neonates <3 kg as well as for term neonates 3–10 kg. However, as noted in that Special Report, “The ratios of trace elements in commercially available pediatric multiple trace element products result in excessive intake of Mn if recommended doses of zinc are given”. Indeed, the recommended intakes of trace elements can only be achieved through the use of individualized trace element supplementation. The use of trace element solutions with fixed ratios of multiple components (Zn, Cu, Mn, Cr) limits flexibility that may be needed to regulate Mn intake (or that of other trace elements) under various clinical conditions, such as cholestatic liver disease or Fe-deficiency, particularly in vulnerable populations, such as neonates.

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Abbreviations:

CNS	central nervous system
DMT-1	divalent metal transporter 1
EAR	estimated average requirement
ESAADI	estimated safe and adequate dietary intake
IPD	idiopathic Parkinson’s disease
Mn-SOD	Mn superoxide dismutase
NAS	National Academy of Sciences
NIEHS	National Institute of Environmental Health and Safety
NRC	National Research Council
RDA	recommended dietary allowance
ROS	reactive oxygen species
TPN	total parenteral nutrition
Tf	transferrin

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Table 1

Manganese content of human milk and infant formulas

	Human milk	Cow formula	Soy formula
Mn content	3–10 µg/l	30–50 µg/l	200–300 µg/l

Table 2

Content and intake of manganese in human milk versus Mn-supplemented infant total parental nutrition (TPN)

	Human milk	TPN (Mn-free)	Multitrace®-4
Mn content	3–10 µg/l	5.6–8.9 µg/l	25 µg/ml
Mn intake (based on 150 ml/kg/day)	0.45–1.5 µg/kg/day	0.84–1.34 µg/kg/day	5.0–7.5 µg/kg
Absorption	8%	100%	100%
Mean Mn burden	0.06 µg/kg/day	1.0 µg/kg/day	5.0–7.5 µg/kg/day