Manganese in Parenteral Nutrition: Who, When, and Why Should We Supplement?

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Micronutrient requirements are not fully understood. Parenteral nutrition (PN) usually contains the trace element (TE) manganese (Mn) from fixed-concentration TE supplements. Multiple TE formulations may not be optimal in pediatric and home PN. Moreover, most PN products contain Mn as a ubiquitous contaminant. Excessive Mn can lead to Parkinson-like symptoms resulting from hypermanganesemia. A survey of 40 Australasian hospitals that contributed data on 108 patients to the annual home PN register and a systematic review of the literature were conducted to establish the scope of the potential problem of Mn toxicity in PN patients. Exposure to Mn doses 5–6 times current daily requirements, together with the TE contamination that is reported in PN products, can lead to neurotoxicity. Whole-blood levels are more accurate for monitoring and correlate well with signal intensity of magnetic resonance imaging. Current TE formulations restrict prescribing options. The regulatory mechanisms of Mn homeostasis are bypassed via the parenteral route so elimination via the hepatobiliary system is impaired, resulting in tissue or brain accumulation. Published dosage recommendations may be excessive and official guidelines require revision. Variability in clinical practices necessitates that individual TE additives are more widely available and multiple TE products reformulated. More frequent monitoring for any brain accumulation is recommended. The scarcity of PN-associated Mn deficiency, plus the growing evidence for Mn toxicity, leads to the conclusion that it is unnecessary for Mn to be prescribed routinely for pediatric or long-term PN patients.

Micronutrient requirements for parenteral nutrition (PN) are not well understood and guidelines for supplementation are outdated. PN admixtures usually contain manganese (Mn) as part of a fixed-concentration trace element (TE) supplement, but current TE formulations restrict prescribing options. As home PN (HPN) becomes used more routinely, commercial supplements of multiple TE in fixed formulations may not be suitable for long-term use. Excessive doses of TE such as Mn have been associated with liver cholestasis and can lead to symptoms that include insomnia, headache, increased forgetfulness, anxiety, rapid hand movements, and loss of coordination resembling Parkinson's disease. Our recent survey of 40 Australian and New Zealand hospitals contributing to the Australasian Society of Parenteral and Enteral Nutrition Annual HPN Register,[1] together with our own clinical experiences with HPN over many years and a systematic review of the literature, confirm Mn toxicity is a potential problem with adult and pediatric PN patients.

Metabolic Functions of Manganese

Mn is considered to be an essential trace element required as a catalytic cofactor for a variety of important enzymatic reactions. An average adult body has approximately 10–12 mg Mn incorporated into the active center of the various metalloenzymes; arginase, glutamine synthetase, and most notably Mn superoxide dismutase (SOD), which are located mostly in the mitochondria.[2] Routine administration of Mn and other TEs in PN admixtures is recommended by most authoritative guidelines but there is now growing concern that the fixed-dose multi-TE supplements for neonatal/pediatric patients and adults on long-term HPN (>30 days) may lead to toxicity from chronic overexposure. In the past 2 decades there have been numerous incidents of Mn toxicity. More than 50% of HPN patients may have increased blood levels leading to hypermanganesemia, which often is associated with clinically significant cerebral and hepatic complications.[3] Notwithstanding its essentiality for important enzyme functions, exposure to high levels of Mn can lead to neurotoxicity.

Induction of oxidative stress by free radicals has been implicated as a causative factor of neurotoxic damage associated with exposure to Mn (and other TEs). It is well known that Mn accumulates in astrocytes, and in vitro experiments with astrocyte cultures have shown that pretreatment with Mn inhibits the uptake of glutamine, and

Abbreviations used in this paper: ASPEN, American Society of Parenteral and Enteral Nutrition; AuSPEN, Australasian Society of Parenteral and Enteral Nutrition; ESPEN, European Society for Clinical Nutrition and Metabolism; HPN, home parenteral nutrition; Mn, manganese; MRI, magnetic resonance imaging; PN, parenteral nutrition; SOD, superoxide dismutase; TE, trace element.

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hence expression of the messenger RNA coding glutamine transporters. A fascinating theory by Aschner et al[2] that requires further investigation proposes that alterations in glutamine/glutamate cycling in astrocytes, induced by oxidative stress, may be a key mechanism as to how Mn exerts its neurotoxicity.[4]

Mn absorption from the gastrointestinal tract inversely correlates with dietary content. Absorption in neonates and children is greater than in adults, and females appear to absorb more than males. In healthy individuals less than 5% of orally ingested Mn is absorbed. This maintains Mn homeostasis so that high dietary intake is not a problem in the general population.[5] Thus, the amount of Mn in the diet influences the amount absorbed, as well as its elimination in the bile. Once absorbed, Mn is transported to the liver where a small proportion is bound to transferrin but the majority is bound to γ-globulin and albumin. The main pathway for Mn excretion is via the hepatobiliary system: in the liver Mn is removed from the blood and then conjugated with bile, which is secreted into the intestine where a small fraction of Mn is reabsorbed and the remainder is excreted in the feces. More than 90% is excreted via the bile but biliary excretion is poor in neonates and may contribute to increased delivery of Mn to the brain and other tissues. Low bile excretion, therefore, can increase the potential for toxicity. Hepatic dysfunction and cholestasis are suspected risk factors for increased Mn accumulation in the brain,[2] whereas patients with biliary atresia display hypermanganesemia without any increase in dietary Mn intake.[6]

Parenteral Nutrition, Cholestasis, and Manganese

In PN patients the normal intestinal regulatory mechanism is bypassed and the amount of Mn delivered via the intravenous route is 100% bioavailable. In addition, the normal pathway of elimination via the hepatobiliary system frequently is impaired because of PN-associated biliary stasis and obstructive jaundice. This may be especially important for parenterally fed infants who pass little or no stool and often show evidence of hepatic dysfunction and cholestasis.[2] It also predisposes long-term PN patients to tissue accumulation and/or brain deposition of Mn, resulting in neurologic symptoms. However, a clear cause–effect relationship between PN-associated cholestasis and neurotoxicity has not been established and data about the temporal relationship between the dose and duration of Mn supplementation and increased Mn levels have been to some degree contradictory.[7]

In Australia, Ali et al[8] evaluated the serum Mn levels of 8 long-term adult HPN patients over a 4-month period to determine if there was any correlation with liver cholestasis. The patients were receiving a commercial multiple TE preparation providing 0.3 mg (5 μmol) Mn per day 3 times per week. Serum levels of liver enzymes, such as alanine aminotransferase (ALT), γ-glutamyltransferase, bilirubin, urea, creatinine, and a calculated glomerular filtration rate were obtained at the same time. Occurrence of cholestasis was determined by the senior gastroenterologist when increased bilirubin greater than 70 μmol/L and increased ALT, γ-glutamyltransferase, and aspartate aminotransferase were considered as biochemical evidence of cholestasis. Half of this small cohort of patients showed hypermanganesemia irrespective of the presence of cholestasis and/or duration of PN. One patient had high serum Mn levels with very mild increases of liver enzyme levels, 2 patients displayed increased serum Mn levels with normal liver enzyme levels, and 1 patient had below normal Mn levels with biochemical evidence of cholestasis. Mn supplementation was discontinued in 3 patients with increased serum levels. Subsequent blood tests showed serum levels eventually decreased and normalized over a 5- to 6-month period. No correlation existed in these adults between increased Mn and the indices of cholestasis.

These clinical experiences are supported by the recent infant study of McMillan et al.[9] Cholestasis was not deemed to be a significant predictor of Mn status in their assessment of 54 pediatric PN patients. Of the 20 patients with cholestasis, 13 had normal serum Mn levels, but 13 of 21 patients with high Mn levels had no cholestasis. The investigators found no correlation in their regression model comparing cholestasis as a predictor of high, low, or normal Mn ($P = .7732$). Nevertheless, they strongly recommended that all pediatric patients who develop cholestasis should have Mn levels determined regularly.

Measuring and Monitoring Levels of Manganese

Regular monitoring of patients receiving fixed doses of Mn over prolonged periods is recommended, but plasma and serum analyses are poor indicators of body stores. Balance studies are problematic because of the rapid excretion of Mn into bile, and because studies over short periods do not give results proportional to Mn intakes. A battery of potential biomarkers including lymphocyte Mn-SOD and/or arginase activity has been proposed, but there is no readily available indicator of whole-body Mn status.[10] The recent prospective observational study in pediatric PN patients concluded that there was no correlation between copper and Mn levels and no evidence to support the practice of dosing Mn based on the more reliable determination of serum copper values.[9] Reference intervals of what is considered a normal Mn level vary considerably. Because 60%–80% of Mn is contained in red blood cells,[5] erythrocyte or whole-blood Mn concentrations appear to be the most accurate and reproducible parameter. According to The Auckland reference laboratory, normal Australasian values can range