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Manganese in Human Parenteral Nutrition: Considerations for Toxicity and Biomonitoring

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Abstract

The iatrogenic risks associated with excessive Mn administration in parenteral nutrition (PN) patients are well documented. Hypermanganesemia and neurotoxicity are associated with the duration of Mn supplementation, Mn dosage, as well as pathological conditions, such as anemia or cholestasis. Recent PN guidelines recommend the biomonitoring of patients if they receive Mn in their PN longer than 30 days. The data in the literature are conflicting about the method for assessing Mn stores in humans as a definitive biomarker of Mn exposure or induced-neurotoxicity has yet to be identified. The biomonitoring of Mn relies on the analysis of whole blood Mn (WB Mn) levels, which are highly variable among human population and are not strictly correlated with Mn-induced neurotoxicity. Alterations in dopaminergic (DAergic) and catecholaminergic metabolism have been studied as predictive biomarkers of Mn-induced neurotoxicity. Given these limitations, this review addresses various approaches for biomonitoring Mn exposure and neurotoxic risk.

Keywords

Manganese; Parenteral Nutrition; Biomonitoring; Neurotoxicity

1. Background

Mn is an essential trace element (Kemmerer et al., 1931), required for normal mammalian physiological processes, such as bone growth, development of cartilage and connective tissues (Hurley, 1981), reproductive function (Keen et al., 1999), neuronal function (Sloot and Gramsbergen, 1994; Takeda et al., 1998), immune function, digestion and defense against free radicals (Aschner et al., 2005; Greger, 1999). Mn supplementation in PN patients is essential (Hardy et al., 2008) to prevent the depletion of endogenous stores and symptoms of deficiency (Hardy, 2009). Despite the classification of Mn as an essential trace

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element, there is little evidence in humans of Mn deficiency being clinically relevant (Hardy et al., 2008), as no cases of deficiency have been described in humans receiving un-supplemented PN (Frankel, 1993). Most of the evidence for human Mn deficiency is derived from experimental studies where subjects received Mn depleted diets (Hardy et al., 2008). The first case of suspected Mn deficiency was in a male subject who was fed a chemically defined diet as part of an investigation for determining vitamin-K requirements. Mn was inadvertently omitted from the diet for 17 weeks; the subject developed mild dermatitis, reddening of his black hair and beard, slowed growth of hair, nails, and beard, occasional nausea and vomiting, and moderate weight loss. His total diet (food and water) provided only 0.35 mg Mn/d, resulting in 55 and 85% reduction in serum and stool Mn levels, respectively (Doisy, 1974). Friedman et al. (1987) investigated experimental Mn depletion in seven healthy male subjects, from 19 to 22 years of age. The subjects were fed a Mn-adequate diet (2.59 mg Mn/d) for 3 weeks to establish baseline data followed by a purified diet containing 0.11 mg Mn/d for 39 days (depletion), followed by two 5 day periods of 1.53 and 2.55 mg Mn/d (repletion). The appearance of dermatitis, termed *Miliaria Crystallina* (prickly heat), developed in five of the seven subjects at the end of the depletion period, but disappeared as Mn repletion began (Friedman et al., 1987).

Although, PN was introduced into medical practice in the 1960s (Buchman et al., 2009; Dudrick and Wilmore, 1968), the iatrogenic risk of Mn-induced neurotoxicity associated to PN was only recognized in 1990, when Mehta and Reilly (1990) reported a case of a 32-year old woman medicated with haloperidol, receiving Mn (0.3 mg) daily. After 4 months of Mn supplementation, the patient developed extrapyramidal signs, which were irreversible after haloperidol discontinuation. WB Mn was significantly increased, and 3 days after receiving Mn-free PN all symptoms resolved. WB Mn levels fell to normal limits within 1 month after Mn discontinuation in the PN solution (Mehta and Reilly, 1990).

Mn toxicity upon ingestion is rare as homeostatic mechanisms tightly regulate its absorption and excretion (Santamaria and Sulsky, 2010; Underwood, 1981), ensuring adequate supplies. In contrast, Mn delivered intravenously (IV) bypasses homeostatic mechanisms regulating Mn absorption (Alves et al., 1997; Bertinet et al., 2000; Fitzgerald et al., 1999; Hambidge et al., 1989; Malecki et al., 1996; Mehta and Reilly, 1990; Mirowitz et al., 1991; Reimund et al., 2000). When dietary Mn levels are high, adaptive changes include reduced gastrointestinal (GI) absorption of Mn, enhanced Mn liver metabolism, and increased biliary and pancreatic excretion of Mn (Aschner and Aschner, 2005). For example, when rats were given an oral tracer dose of $MnCl_2$, the amounts found in the stomach, duodenum, and jejunum on a % dose/g tissue basis decreased as dietary Mn increased from 4 to 2000 ppm (Abrams et al., 1976). Some studies suggest that Mn is absorbed through an active transport mechanism (Garcia-Aranda, Wapnir and Lifshitz, 1983), which most likely involves the metal divalent transporter 1, referred as DMT1 (also known as DCT-1 or nramp-2) (Bai et al., 2008). The mechanism underlying the regulation of Mn absorption has not been fully clarified, but an important role has been ascribed to DMT-1 (Garcia et al., 2006; Wang, Li and Zheng, 2006). Mn homeostasis is also believed to be maintained by excretion of excess absorbed Mn through the gut (Davis, Zech and Greger, 1993) as biliary secretion is the main pathway for Mn excretion. Mn biliary elimination is dose-dependent (Malecki et al., 1996).

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The rate of Mn radioactivity elimination following an IV injection of a tracer dose in bile duct ligated rats was enhanced by IV injection of large amounts of unlabelled Mn, indicating inducible intestinal excretion of Mn (Bertinchamps, Miller and Cotzias, 1966). Dose-dependent elimination of tracer doses of Mn has also been reported in Mn-exposed miners from Chile as compared to control populations. The terminal blood half-time for the active (i.e., Mn-exposed) miners was 15 ± 2 days, compared to 37.5 ± 7.5 days for control individuals and 28.3 ± 8 days for ex-miners with chronic Mn toxicity who had stopped working in mining 2 to 25 years previously (Cotzias et al., 1968). There is a limited knowledge on the molecular mechanisms that mediate Mn elimination. Mn concentration in bile can exceed plasma by 100-fold, suggesting active transport (Crossgrove and Yokel, 2004). Recently, solute carrier 30A10 (SLC30A10) has been identified as a human Mn transporter, highly expressed in the liver. The autosomal recessively inherited disorder associated SLC30A10 deficiency leads to Mn accumulation in liver (Tuschl et al., 2013). No studies have been published on the effect of Mn on SLC30A10 expression.

Since the first report of Mn-induced neurotoxicity, numerous other cases of parkinsonian-like symptoms associated with Mn exposure from parenteral admixtures have been reported (Alves et al., 1997; Bertinet et al., 2000; Ejima et al., 1992; Fitzgerald et al., 1999; Mirowitz and Westrich, 1992; Mirowitz et al., 1991; Nagatomo et al., 1999; Hambidge et al., 1989; Hsieh et al., 2007; Iinuma et al., 2003; Komaki et al., 1999; Ono et al., 1995; Reynolds et al., 1994). Tables 1 and 2 show several cases of hypermanganesemia and induced-neurotoxicity in patients fed by the parenteral route.

2. Modulating Factors of Mn Induced Neurotoxicity

Parenteral Mn Dosage—The dosage of parenteral Mn is recognized as an important risk factor for the development of hypermanganesemia and subsequent neurotoxicity. A broad range of daily adult Mn dosages, extending from a low dose of 0.18–0.91 μmol/d (0.01–0.05 mg/d) to a high of 40 μmol/d (2.2 mg/d) (Wretlind, 1972) has been previously recommended. Most of the case reports of Mn intoxication were in adults receiving > 500 μg/d of parenteral Mn (Alves et al., 1997; Dickerson, 2001; Ejima et al., 1992; Ono et al., 1995; Reimund et al., 2000; Taylor and Manara, 1994) or pediatric patients receiving > 40 μg/kg/d (Fell et al., 1996; Reynolds et al., 1994). The above adult dosage is significantly greater than the total estimated Mn absorbed dose of ~115 μg/d from food and drinking water, and 0.5 μg/d from inhaled Mn (ATSDR, 2000; Santamaria and Sulsky, 2010).

Duration of Mn Supplementation—Several reports describe an association between long-term PN and increased WB Mn levels (Alves et al., 1997; Iinuma et al., 2003; Komaki et al., 1999; Siepler et al., 2003) and brain Mn accumulation, particularly in the basal ganglia. Recent *in vivo* studies suggest that dopamine active transporter (DAT) plays an important role in Mn accumulation in the striatum (Erikson et al., 2005). Inhibition of DAT function in weanling male Sprague–Dawley rats attenuates Mn accumulation in the *globus pallidus* during chronic exposure (Anderson et al., 2007).

Increased brain Mn levels can be detected by T1-weighted magnetic resonance imaging (MRI) (Iinuma et al., 2003). A recent analysis of *post-mortem* data describes the cumulative

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effect of Mn supplementation in patients who received long-term PN for short bowel syndrome (SBS) (Howard et al., 2007). Hypermanganesemia may also be observed after a short course of PN, in patients receiving > 500 μg daily; for example, elevated Mn levels in red blood cells (RBC) of 2 patients were detected after 14 and 18 days of PN (Fitzgerald et al., 1999). These findings suggest a potential toxicity from the administration of high Mn doses in PN and argue that the routine addition of doses higher than 500 μg daily may pose a risk of Mn-induced neurotoxicity even after short-term administration.

Co-morbidities associated with Mn exposure—Hypermanganesemia can occur as a result of liver disease and decreased biliary excretion (Ikeda et al., 2000), as bile is the major excretory route for Mn. Patients on long-term PN may develop biliary stasis or obstructive jaundice (Angsten et al., 2012; Fallon et al., 2010; Graham et al., 1984; Jones et al., 1993; Pierro et al., 1989; Sax et al., 1986; Shattuck et al., 1993), resulting in excess tissue Mn accumulation (Alves et al., 1997; Fell et al., 1996; Ikeda et al., 2000; Witzleben et al., 1968). Elevated Mn levels have also been seen in patients suffering from chronic liver failure (with inability to excrete Mn via the biliary system) and undergoing PN supplementation (McKinney et al., 2004; Mehta and Reilly, 1990).

Iron (Fe) deficiency (ID) can increase brain Mn levels (Heilig et al., 2005), as it is associated with high concentrations of serum transferrin receptors (TfR) (Kivivuori et al., 2000; Punnonen et al., 1994), which are transporters present at the blood-brain barrier (BBB) that mediate brain influx of both Fe and Mn (Aschner and Aschner, 1991; Erikson et al., 2002).

Animal studies have demonstrated that ID enhances Mn absorption across the GI tract, independent of body Mn stores (Chandra and Shukla, 1976; Shukla et al., 1976). An inverse association has been also demonstrated between DMT1 levels and Mn absorption in humans (Finley and Davis, 1999). Competition between Mn and Fe for intestinal absorption likely occurs by way of DMT1 (Aschner et al., 2005; Bai et al., 2008; Rouault and Cooperman, 2006). DMT1 expression is regulated by Fe status (Thompson et al., 2007) and its levels greatly increase in the duodenum in response to ID (Gunshin et al., 2001). DMT1 is also present in the plasma membranes of astrocytes (Au et al., 2008). Erikson and Aschner (2006) showed that increased Mn uptake in primary astrocyte cultures, with altered Fe status is mediated primarily DMT-1 (Erikson and Aschner, 2006).

3. Toxicological Evaluation Mn Levels in PN

Levels of safe and adequate quantities of Mn in PN are not known (Alves et al., 1997). PN guidelines are based on a Mn oral reference dose (RfD) considering also Mn bioavailability by the oral route. The United States Environmental Protection Agency (US EPA, 1996) used estimates of Mn levels in typical western and vegetarian diets to calculate Mn RfD in food. The RfD represents an estimate of the daily exposure to which the human population (including sensitive subpopulations) may be continually exposed over a lifetime without an appreciable risk of deleterious effects (Goldhaber, 2003).

The RfD for Mn was calculated by dividing the no-observed-adverse-effect level (NOAEL) by the product of the total amount of uncertainty and modifying factors that reflect the

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limitations of the data used (Nance, 2005). The NOAEL is the highest experimental dose at which there is no statistically or biologically significant increase in frequency or severity of adverse health effects, as seen in the exposed population compared with an appropriate unexposed population (ECETOC, 2002). In contrast to numerous reports describing Mn toxicity following inhalation exposure at high doses in humans, there are relatively few reports on manganism arising from water or dietary sources. Four studies have reported toxicity from ingestion of drinking water containing high levels of Mn. Kawamura and coworkers (1941) documented outbreaks of manganism in Japan and Greece, respectively, due to consumption of well-water contaminated with extremely high levels of Mn (1.8 to 14 mg/L) (Kawamura et al., 1941). Wasserman and coworkers (2006, 2011) also reported adverse impact of Mn exposure associated with water consumption on child developmental outcomes in Bangladesh (Wasserman et al., 2006; Wasserman et al., 2011). In another study, neurologic symptoms were reported in individuals who consumed drinking water containing Mn levels of 1.8–2.3 mg/mL in Greece (Kondakis et al., 1989). Mn toxicity has been reported in an individual who consumed high amounts of Mn supplements for several years (Banta and Markesbery, 1977). In animals, the toxicity of ingested Mn is low and signs of a toxic response generally appear only after concentrations higher than 1,000 μg/g diet are consumed (Hurley, 1981).

Based on a composite of data from several epidemiological studies, the NOAEL was derived at 10 mg/d (0.14 mg/kg/d for 70 kg adult) for chronic human consumption of Mn in the diet (US EPA, 1996). However, the US EPA stated that there are significant concerns about possible adverse neurological effects at doses not far from the range of essentiality. Because of this concern, the US EPA recommended that a modifying factor of 3 be applied when assessing risk from Mn in drinking water or soil. A modified RfD of 0.05 mg/kg/d is recommended for Mn from drinking water or soil (Goldhaber, 2003).

The Mn acceptable daily intake (ADI) was established based on median intake because data are insufficient to calculate the recommended dietary allowance (RDA) (Gropper and Smith, 2013). Progress in the field of Mn nutrition has been hampered because of the lack of a practical method for assessing Mn status as inter-individual variations in Mn retention can be large (Davidsson et al., 1989). Blood Mn levels appear to reflect body Mn status of rats fed deficient or adequate amounts of Mn (Keen et al., 1983), but consistent changes in blood or plasma Mn levels have not been observed in depleted or repleted human subjects (Freeland-Graves et al., 1988; Friedman et al., 1987).

The US National Research Council (NRC) has established an estimated safe and acceptable dietary intake (ESADDI) of 2–5 mg/d for adults (Greger, 1998). The first guidelines for Mn supplementation in PN were developed by the American Medical Association Nutrition Advisory Group (AMA NAG) (AMA, 1979). In 1988, the pediatric parenteral trace element requirements were reevaluated by the Committee on Clinical Practice Issues of the American Society for Clinical Nutrition (ASCN) and the pediatric dosage of Mn was reduced to 1 μg/Kg/d (from 2 to 10 μg/Kg/d) about 10 years after the original AMA NAG recommendations were published (Greene et al., 1988). The European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for

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Clinical Nutrition and Metabolism (ESPEN) recommended 1μg/kg/d with a maximum of 50 μg/d for children receiving long-term PN (Koletzko et al., 2005).

In 2002, the published literature indicated a broad range in adults Mn supplementation in PN. Takagi et al. (2002) suggested a safe optimal Mn dose for adult patients undergoing PN at 1 μmol/d based on MRI observations (Takagi et al., 2002). Later, in 2004 the AMA guidelines were revisited by the American Society of Parenteral and Enteral Nutrition (ASPEN) and the daily intake of Mn for adults was reduced to 60–100 μg/d (Mirtallo et al., 2004). Although based on toxicological data, the Mn levels suggested in the recent ASPEN guidelines do not pose a significant risk for Mn overexposure in patients without risk factors, other sources of exposure should be considered in PN patients, such as the contamination of PN with Mn from raw components of PN (Buchman et al., 2009; Dickerson, 2001; Jetton et al., 1976; Malecki et al., 1996). Table 3 summarizes the guidelines issued for the parenteral administration of Mn.

4. Biomonitoring of Mn in Patients Undergoing PN

Biomonitoring is based on a systematic collection of biological samples for analysis of concentrations of compounds, metabolites or specific non-adverse biological effect parameters, with the objective of assessing exposure and health risk in exposed subjects, comparing the data observed with the reference level and — if necessary — leading to corrective actions (Zielhuis, 1984). The World Health Organization (WHO) defined a biomarker as a chemical, its metabolite, or the product of an interaction between a chemical and some target molecule or cell that is measurable in the human body (WHO, 2006). Biomarker research assumes that toxicant-induced diseases are progressive and that injury proceeds from entry of the toxicant into target cells, which induces subcellular biochemical events, to cell- and organ-level events that eventually induce irreversible or persistent organism dysfunction (Silbergeld and Davis, 1994); such effect markers are generally preclinical indicators of abnormalities (Grandjean and Landrigan, 2006) (Figure 1).

Biomarkers may be classified into three types: biomarkers of exposure (internal dose), of effect or of susceptibility (Amorim, 2003; Costa, 1996). Exposure biomarkers reflect the internal dose of a xenobiotic and may be an exogenous compound (or a metabolite) within the body, an interactive product between the compound (or metabolite) and an endogenous component, or another event related to the exposure (Grandjean and Landrigan, 2006). A biomarker of effect is a characteristic that can be objectively measured and evaluated as an indicator of normal or pathogenic biologic processes (Atkinson, 2001).

Biomarkers of susceptibility serve as indicators of a particular sensitivity of individuals to the effect of a xenobiotic or to the effects of a group of such compounds (Gil and Pla, 2001). Biochemical events can be modified by genetically determined individual differences which may play a role as modifiers not only of long-term outcomes, but also of early biochemical changes. Examples of biomarkers of individual susceptibility to Mn include Fe status and markers of redox status (Smargiassi and Mutti, 1999), the latter playing a key role in Mn neurotoxicity.

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4.1. Classical Approach of Mn Biomonitoring in PN Patients: Biomarkers of Exposure

Mn concentrations in Body Fluids—WB Mn levels are linked to the external administration of Mn by the PN route; for example a study in adult patients receiving PN showed that WB Mn changed in a dose-dependent manner. Takagi et al. (2002) reported that WB Mn was significantly higher when PN patients were administered 2 or 20 μmol Mn/d compared to 0 or 1 μmol/d during PN exposure (Takagi et al., 2002).

A reasonable biomarker of Mn exposure should display an acceptable threshold or cut-off value above which a Mn exposed individual can be differentiated from unexposed individuals (Zheng et al., 2011). Although WB Mn analysis is the preferred screening method, the high variability in normal human Mn levels makes it unsuitable for individual biological monitoring (Apostoli et al., 2000). A review by Iyengar and Woittiez (1988) reported median Mn values of 13.6 (8.0–18.7) μg/L in WB, 0.63 (0.54–1.76) μg/L in serum and 0.6 (0.5–9.8) μg/L in urine from a population covering 100,000 individuals from 55 countries (Iyengar and Woittiez, 1988). A comprehensive review on Mn from the USA quotes 4 – 15 μg/L for WB, whereas a more recent North American publication quotes a slightly higher range of 7– 16 μg/L as the normal levels in WB (Hardy et al., 2008). Albeit the high variability in WB Mn levels, a community based study in Québec showed an association between higher WB Mn (above 7.5 μg/L) levels and motor deficits (Mergler et al., 1999).

The utility of serum Mn has been questioned as a marker for whole body Mn as it was reported that intra-cerebral Mn levels were elevated in the presence of normal serum values (Alves et al., 1997). Several authors do not consider serum and WB Mn levels to be suitable indicators and suggest that the Mn content of RBCs may better reflect tissue accumulation as it is not directly influenced by current IV supplementation. WB matrix and WB Mn level is affected by IV delivery of Mn (Keen et al., 1983). Accordingly, in patients receiving PN, WB Mn is influenced by the pattern of PN (i.e. intermittent PN vs. continuous whole-day PN), as it may lead to changes in the distribution of Mn between tissues and blood and result in individual variation in response to parenterally administered Mn (Iinuma et al., 2003). RBC accounts for about 60–80% of Mn in the WB (Buchet et al., 1976; Hagenfeldt et al., 1973; Mirowitz et al., 1991), their turnover is slower than that of other cellular components (Milne et al., 1990) and RBC Mn levels are not directly dependent on current IV supplementation which makes them better indicators of Mn exposure (Bertinet et al., 2000).

Urinary Mn levels may also serve as a biomarker of exposure. However, biliary excretion is the main pathway by which Mn is excreted with most of the element ultimately being excreted in the feces (Aschner et al., 2005; Davis et al., 1993). Urinary Mn excretion is low, representing only about 0.01 ± 1% of the absorbed dose (Apostoli et al., 2000), and about 6% of the total excreted amount (Smargiassi and Mutti, 1999). Greger et al. (1990) and Davis and Greger (1992) failed to demonstrate a correlation between urinary Mn concentration and dietary intake in adult male and female volunteers (Davis and Greger, 1992; Greger et al., 1990). Mn in urine shows a poor correlation with either recent or cumulative dose (Lucchini et al., 1995; Smargiassi and Mutti, 1999).

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Magnetic Resonance Imaging (MRI)—MRI intensity in the *globus pallidus* is a useful means for the detection of brain Mn accumulation (Finkelstein et al., 2008; Takagi et al., 2002). The Mn (II) ion has five unpaired electrons in the 3d orbit, causing the shortening of T1-relaxation time and an increase in signal intensity on T1-weighted MRI (Kim, 2004). In clinical settings, most patients undergoing PN are asymptomatic and diagnosed only on the basis of abnormal T1 signal intensity in the *globus pallidus* and occasionally in the tegmentum of the brainstem (Mirowitz et al., 1991; Saitoh et al., 1996).

4.2. Alternative Approaches: Subclinical Biomarkers predictive of Mn-induced Neurotoxicity

Neurobehavioral Tests—During the early stages of pathogenesis, Mn-induced neuropsychological impairment is subtle (Bowler et al., 2007; Mergler and Baldwin, 1997; Roels et al., 1987), characterized by alterations in motor function and response speed, as well as memory and more complex cognitive function impairments (Bowler et al., 2003; Laohaudomchok et al., 2011; Sinczuk-Walczak et al., 2001). The first manifestations of poisoning by Mn are usually subjective (Emara et al., 1971) (Figure 2). Biomarkers should provide information about neurotoxic effects-induced by Mn, as the preliminary early neurotoxic effects are subtle (Mergler and Baldwin, 1997), as they usually precede the emergence of more serious adverse effects. Neurophysiological assessments rely on sensitive tools to assess neurophysiological functions and neuropsychological performance; Mn exposure may lead to poorer hand-eye coordination, motor slowing, increased tremor, reduced response speed, olfactory enhancement, mood changes and possible memory and intellectual deficits (Iregren, 1994; Mergler et al., 1999).

Neuroimaging Biomarker: ^{1}H proton magnetic resonance spectroscopy (^{1}H MRS)—Recent studies with ^{1}H proton magnetic resonance spectroscopy (^{1}H MRS), a noninvasive technique used for studying brain metabolites (Zheng et al., 2011), show an increase in γ-aminobutyric acid (GABA) content in the thalamus region of smelters occupationally exposed to Mn (Dydak et al., 2011). Classically, Mn neurotoxicity is characterized by deregulation of glutamatergic (Bagga and Patel, 2012; Garcia et al., 2006), GABAergic (Bagga and Patel, 2012; Erikson et al., 2002; Fitsanakis et al., 2006; Stanwood et al., 2009) and dopaminergic (DAergic) systems (Fitsanakis et al., 2006; Stanwood et al., 2009). Striatal GABA concentrations in rats are altered after long-low exposure to Mn (Gwiazda et al., 2002). Conflicting data exists as to whether Mn accumulation leads to decreases or increases in regional GABA levels (Erikson et al., 2002; Fitsanakis et al., 2006). For example, exposure to 6 mg Mn/kg/d led to a significant increase in brain Mn concentrations and significant decrease in GABA concentrations (Chandra et al., 1982). Another report showed that rats exposed to 20 mg Mn/kg/d had significantly increased brain Mn and GABA concentrations (Lipe et al., 1999). Accordingly, it appears that a relationship exists between the severity of Mn exposure and GABA concentrations, with lower Mn exposure leading to decreased GABA, and higher Mn exposure leading to increased GABA concentrations (Erikson et al., 2002; Fitsanakis et al., 2006). Further research is needed to study the effect of Mn exposure on GABA content in populations with higher risk of developing Mn-induced neurotoxicity before applying this methodology to biomonitor PN patients.

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Hematologic and Urinary Biomarkers related to catecholaminergic system— Research strategies in development for a biomarker of Mn-induced neurotoxicity have focused mainly on the effects of Mn on the DAergic and GABAergic systems (Calabresi et al., 2001). Several studies reported alterations in homovanillic acid (HVA) (Ai et al., 1998; Siqueira and Moraes, 1989) and vanillylmandelic acid (VMA) (Ai et al., 1998) levels in populations exposed to higher Mn levels (Table 4). In humans, VMA is the major end product of norepinephrine and epinephrine metabolism, whereas HVA is the main end product of dopamine (DA) metabolism (Eisenhofer et al., 2004; Kvetnansky et al., 2009). The high prevalence of increased HVA levels suggest an increased activity of monoamine oxidase B (MAO B) (Smargiassi and Mutti, 1999). However, this finding was not replicated in a separate study of 11 men randomly selected in a ferromanganese-alloy plant, where a tendency towards lower platelet MAO B activity was found in the exposed workers (Smargiassi et al., 1995). MAO B cannot be recommended for monitoring early biochemical events of Mn exposure as platelet MAO B activity can be modified by genetically determined individual differences (Smargiassi and Mutti, 1999), such as differences in the genotype of transcription factor AP-2 beta (Pivac et al., 2006). Mn also affects dihydropteridine reductase (DHPR) activity, an enzyme required for regeneration of the cofactor tetrahydrobiopterin (BH4), an essential cofactor in enzymes involved in aromatic amino acid hydroxylation, such as phenylalanine and tyrosine hydroxylases (Butler et al., 1978). Altindag et al. (2003) found that Mn in the sulfate form, led to statistically significant decreases in DHPR activity (Altindag et al., 2003). These results are also consistent with a previous study from our group where we noted increased tyrosine and phenylalanine levels in the brains of rats exposed to Mn (Santos et al., 2012).

Mn exposure in monkeys (Dydak et al., 2011) and rats (Fitsanakis et al., 2008) reduces striatal DA content. The DAergic function can also be assessed indirectly by measuring prolactin levels (Takser et al., 2004), as DA is produced by tubero-infundibular neurons and is the major factor controlling prolactin synthesis and release. Once taken up by the capillaries of the hypophysial portal system, DA acts directly on pituitary and neuronal DA receptors to inhibit prolactin secretion (Chang and Shin, 1997). Table 4 shows data from several studies in which prolactin levels were used to assess Mn-induced neurotoxicity (Alessio et al., 1989; Montes et al., 2008; Roels et al., 1992; Smargiassi and Mutti, 1999; Takser et al., 2004).

5. Summary

PN guidelines recommend the biomonitoring of patients if they receive Mn with their PN for >30 days (Mirtallo et al., 2004). The data in the literature are conflicting about the best method for assessing Mn stores in humans and a definitive biomarker of Mn exposure or induced-neurotoxicity has not been identified or validated. Biomarkers of Mn exposure, such as WB Mn levels, are of limited use in evaluating Mn-induced neurotoxicity. Accordingly, periodic brain MRI examination may be required to monitor excess Mn accumulation in the brain of patients receiving PN (Iinuma et al., 2003). However, MRI is not used as a routine method for diagnosis due to high costs and accessibility. Furthermore the relationship between hyperintensities in the basal ganglia and the onset of subclinical Mn neurotoxicity has yet to be determined (Finkelstein et al., 2008). Several authors also

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suggest that Mn accumulation detected by MRI does not necessarily correlate with the degree of clinically apparent neurological abnormalities (Masumoto et al., 2001). RBC Mn concentrations appear to be a promising biomarker of Mn exposure. Mn and Fe share similar transport mechanisms in cells of erythroid tissue, duodenal mucosa, kidney and blood-brain barrier (Chua and Morgan, 1997). The mechanisms of Mn transport into erythroid cells were investigated using rabbit reticulocytes and mature erythrocytes. High affinity Mn^{2+} transport occurred in reticulocytes, but not erythrocytes with K_m of 0.4 μM. Low affinity Mn^{2+} transport occurred in erythrocytes as well as in reticulocytes and had K_m of ~20 and 50 μM for the two cell types, respectively. The direction of Mn^{2+} transport was reversible, resulting in Mn^{2+} efflux. The uptake of Mn-Tf occurred only with reticulocytes and was dependent on receptor-mediated endocytosis (Chua et al., 1996). The permeability constant for inward and outward movement of Mn(II) in mature normal human RBC are $2.87 \pm 0.13 \times 10^{-9}$ and $1.38 \pm 0.21 \times 10^{-9}$ cm./sec, respectively. This slower rate of outward movement is consistent with the finding that 40 to 60 per cent of the Mn(II) taken up by the RBC is non-ultrafilterable. Less than 5 to 10 per cent of the Mn(II) appears to be bound to the stroma. This findings suggest that the entry and exit of Mn(II) is a process of passive diffusion involving no carriers, transport, or metabolic linkage (Weed and Rothstein, 1960). Research is needed to ascertain the relationship between Mn exposure and the impact in different exposure indices such as RBC, WB and urine Mn. Additional research is also needed to establish the putative relationships between Mn exposure, internal dose and alterations in neurotransmitter metabolites (HVA, VMA) and prolactin.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Hypermanganesemia and neurotoxicity are associated with the duration of Mn supplementation.
- Whole blood Mn levels are not well correlated with Mn-induced neurotoxicity.
- This review addresses various approaches for biomonitoring Mn exposure and neurotoxic risk.

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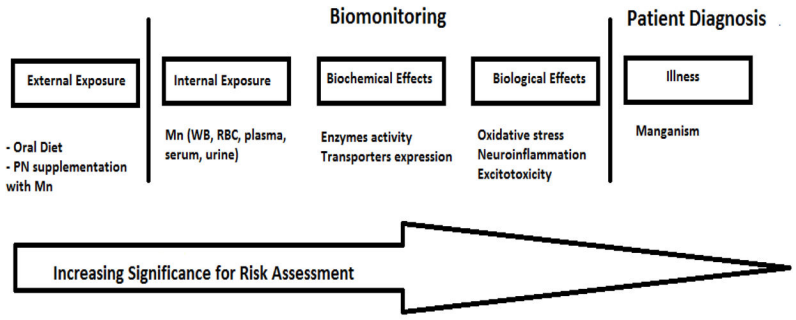

Figure 1.
Biomonitoring paradigm of Mn in patients undergoing PN

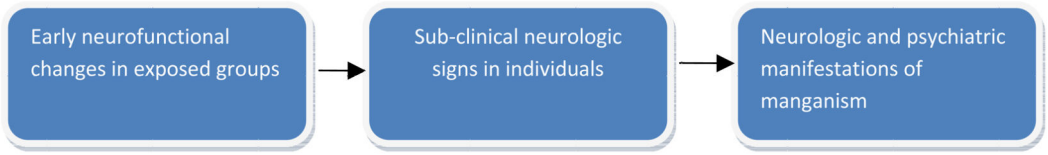

Figure 2.
Progression of neurofunctional changes in response to Mn exposure (adapted from Mergler et al., 1997).

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Table 1

SELECTED REPORTS OF HYPERMANGANESEMIA IN PARENTERALLY FED ADULT PATIENTS

Reference	n	Age Range	Disease	Mn daily dose and duration of intake	Laboratory Findings	Radiological Findings	Clinical Symptoms
Ejima et al. (1992)	1	62 y	SBS	2.2b mg (2.3 mo)	Incr WB Mn 3.0–5.6 μg/dL (normal range 0.4–2.0), decr after 15 wk of Mn-free PN	Incr MRI signal (basal ganglia, especially globus pallidus, tectum, and tegmentum of midbrain and pons); MRI signal decr after 22 wk of Mn-free PN.	Parkinsonism w/dysarthria, mild rigidity, hypokinesia, masked face, halting gate.
Mirowitz et al. (1991)	9	51–74 y	numerous	0.3–0.4 mg (mean PN duration 5.3 y, range 5 mo–11 y)	NR	Incr MRI signal (basal ganglia)	5 pts w/neurologic symptoms: memory loss, confusion weakness, fatigue and imbalance.
Mirowitz and Westrich (1992	1	61 y	GI dyskinesia	0.4 mg (PN duration 3 y)	NR	Incr MRI signal (globus pallidus); 12 mo after d/c Mn, complete regression MRI signals	No symptoms
Alves et al. (1997)	1	63 y	SBS	1–2 mg (PN duration 19 mo)	Incr serum Mn 114 nmol/L (normal range 10–40) and incr urine Mn 381 nmol/L (normal range 15–60 nmol/24 h)	Incr MRI signal (basal ganglia and white matter); 6 mo after d/c Mn, decr MRI signals	Gait disturbance, dystonic movements
Nagatomo et al. (1999)	1	68 y	ulcerative colitis	20 μmol (PN duration 3 mo)	Incr serum Mn 4.2 mg/dL (normal range 0.4–2.0 mg/dL) and incr urine Mn 9.0 mg/dL (normal range <2.0 mg/dL)	Incr MRI signal (basal ganglia)	Psychiatric symptoms and gait disturbance
	1	70 y	aspiration pneumonia	20 μmol (PN duration 4 mo)	Incr serum Mn 5.1 mg/dL; urine Mn 1.0 mg/dL	Incr MRI signal (basal ganglia)	Progressive gait disturbance and confusion
Fitzgerald et al. (1999)	36	NR	numerous	500 μg (< 48h)	RBC Mn: low to normal	3 selected cases of abnormal MRI	1 pt was noted to exhibit petit mal seizures, vertigo, gait disturbances and peripheral neuropathy
	30	NR		500 μg (range 3–30 d)			
	21	14–87 y		500 μg (range 36–5075 d)	Incr RBC Mn in 15/21 pts in pts w/PN > 37 d (normal range 11 to 23 μg/L)		
Bertinet et al. (2000)	15	32–74 y	numerous	Median Mn suppl. 0.1 mg (median PN duration 3.8 y)	Decr WB Mn after 1 y of IV Mn withdrawal	10/15 incr MRI signal (basal ganglia) at the beginning of the PN	No symptoms

Conc-concentration, d/c - discontinuation, Decr - decreased, GI - gastrointestinal, h-hours, Incr - increased, mo - month, MRI - magnetic resonance imaging, NR - not reported, PN - parenteral nutrition, pts-patients, RBC - red blood cells, SBS - short-bowel disease, suppl. - supplementation, wk - weeks, w/o - without, w/- with, wt - weight, y-years.

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Table 2

SELECTED REPORTS OF HYPERMANGANESEMIA IN PARENTERALLY FED CHILDREN AND ADOLESCENT PATIENTS

Reference	n	Age Range	Disease	Mn daily dose and duration of intake	Laboratory Findings	Radiological Findings	Clinical Symptoms
Fell et al. (1992)	57	1–162 mo	Numerous 46/57 w/o cholestasis	wt<10 Kg-1 µmol/Kg wt>10 Kg-0.8 µmol/Kg (median PN duration 1.25 mo)	45/57 Incr WB Mn 615–1840 nmol/L (normal range 72–210 nmol/L); Higher Mn associated w/cholestasis.	2 selected cases of abnormal MRI Incr MRI signal (globus pallidus, nuclei subthalamic)	2 pts w/dystonic limb movements and abnormal posturing; 4 pts died
Reynolds et al. (1994)	1	7 mo	SBS, PN associated liver disease	44–55 µg/Kg (PN duration 17 mo)	Incr WB Mn 1740 nmol/L (normal range 73–210 nmol/L).	MRI abnormalities compatible w/ deposition of a paramagnetic metal	Developmental delay, abnormal dystonic movements of both arms, microcephaly
	53	NR	numerous	44–55 µg/Kg (PN duration > 6 wk)	Incr WB Mn in 35/53 w/evidence of cholestatic liver disease > 360 nmo/L	NR	NR
Ono et al. (1995)	1	5 y	Intractable diarrhea and recurrent pancreatitis	10 µmol (PN duration > 2y)	Incr WB Mn 135 µg/dL (normal range 14.6 + 4.7), 5 mo after d/c Mn, decr WB Mn to 20 µg/dL	Incr MRI signal (basal ganglia)	Nonspecific headache and amnesia
Komaki et al. (1998)	1	2 y	Intractable vomiting and diarrhea	82 µg/Kg (PN duration 14 mo)	Incr WB Mn 9.7 µg/dL (normal range < 2.5 µg/dL), 3 mo after d/c Mn, decr WB Mn to normal levels	Incr MRI signal (globus pallidus, thalamus), 3 mo after d/c Mn MRI abnormalities regressed	Tremor and generalized tonic seizures, psychomotor retardation, hyperactivity; 3 mo after d/c Mn, seizures and tremor completely disappeared
Hsieh et al. (2007)	1	10 y	SBS	8 µg/kg (PN duration 3 mo)	Incr WB Mn 3.7 µg/dL (normal range 0.4 – 1.4 µg/L)	Incr MRI signal (basal ganglia)	Tonic-clonic seizures
Iinuma et al. (2003)	7	41–249 mo (mean 93 mo)	numerous	15.7–91.5 µg/kg (PN duration 18–37 mo)	4/7 Incr WB Mn 3.1–5.1 µg/dL (normal range 1.8–2.4)	6/7 pts incr MRI signal, 12 mo after d/c Mn, 5/7 pts decr MRI signals	No symptoms

Conc-concentration, d/c - discontinuation, Decr - decreased, GI - gastrointestinal, h-hours, Incr - increased, mo - month, MRI - magnetic resonance imaging, NR - not reported, PN - parenteral nutrition, pts-patients, RBC - red blood cells, SBS - short-bowel disease, suppl. - supplementation, wk - weeks, w/o - without, w/- with, wt - weight, y-years.

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Table 3

GUIDELINES ISSUED FOR ADMNISTRATION OF Mn BY PARENTERAL ROUTE

AMA (1979)	Children	2–10 μg/kg/d
	Adults	0.15and 0.8 mg/d
ASCN (1988)	Infants (pre-termand Term) and Children	1 μg/Kg/d
ASPEN(2004)	Infants (pre-termand Term) and Children	1 μg/Kg/d
	Adults	60–100 μg/d

AMA: American Medical Association ASCN: American Society for Clinical Nutrition ASPEN: American Society of Parenteral and Enteral Nutrition

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Table 4

BIOCHEMICAL BIOMARKERS OF Mn-INDUCED NEUROTOXICITY

Study	Study Population	Alterations in the exposed population
Ai et al. (1998)	Male welders (n=39), control group: non-occupationally exposed to Mn (n=19)	Incr HVA and Incr VMA (sig)
Siqueira and Moraes (1989)	Male workers occupationally exposed to Mn in a ferromanganese alloy plant (n=40), control group: non-occupationally exposed to Mn (n=25)	HVA levels not sig. different among the groups
Montes et al. (2008)	Population living close to a mine and mineral processing plant in Mexico (n=300)	Positive correl. (sig) prolactin and WB Mn
Alessio et al. (1989)	Male workers employed in a ferrous-Mn foundry (n=14), control group: non-occupationally exposed to Mn (n=14)	Incr Prolactin (sig)
Buchet (1993)	Male workers exposed to Mn-containing dust in a dry alkaline battery plant or an Mn oxide and salt producing plant (n=68), control group: non-occupationally exposed to Mn (n=35)	Positive correl. (sig) HVA and urine Mn
Roels et al. (1992)	Male workers (n=92) in a dry alkaline factory, exposed to MnO_2, control group: non-occupationally exposed to Mn (n=101)	Incr Prolactin (not sig)
Takser et al. (2004)	Pregnant women at delivery (n=87)	Positive correl. (sig) prolactin and Mn cord blood levels

Sig - significant, correl-correlation; incr - increased; Decr - decreased