Case report

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Manganese toxicity in critical care: Case report, literature review and recommendations for practice

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Abstract

We present the case of a 62-year-old man on the intensive care unit with pancreatitis. Since early in his admission, and for the remainder of his prolonged stay in intensive care, he has received parenteral nutrition for intestinal failure. The whole blood manganese concentration was significantly increased after 2½ months of parenteral nutrition (PN). Three months into his stay, he developed a resting tremor and extra-pyramidal dyskinesia. In the absence of other neurological symptoms, and with no history of essential tremor, Parkinsonism or cerebral signs, hypermanganesaemia was presumed to be the cause. We review manganese metabolism and toxicity in patients who are fed with parenteral nutrition and review the current recommendations and guidelines.

Keywords

Parenteral nutrition, critical care, manganese toxicity, monitoring

Introduction

Manganese (Mn) is a silvery-grey paramagnetic metal used widely in the processing of other metals. It is an essential trace element, found in a wide variety of dietary sources, including meat, fish, poultry, dried fruit, tea and nuts. Deficiency is very rare in humans because the requirements are very low. Mn is routinely added to parenteral nutrition (PN) solutions. However, the requirements for Mn in PN are not known.

Intravenous delivery of Mn bypasses the homeostatic regulatory feedback control mechanism of the liver and gut. Accumulation of Mn is therefore a risk in patients treated with PN, and in patients who are cholestatic.

Case presentation

A 62-year-old man was admitted to the intensive care unit (ICU) with acute pancreatitis and intestinal insufficiency. He initially required multi-organ support, and has required PN throughout his stay because of fistulating intestinal disease. He has currently been on ICU for over six months.

PN was started on the day of his ICU admission. Standard Mn supplementation was given in the multi-trace element (MTE) preparation Additrace® consisting of Mn, zinc, copper, chromium and selenium, providing 270 µg of Mn per day. After 2 1/2 months of PN, he developed a short-lived, intermittent bilateral tremor. The episodes of tremor start at rest lasting for 15–30 s, initially distally and bilaterally then spreading to all four limbs. They occur most days, varying in frequency and sometimes occur in quick succession. He was referred for a neurology opinion; with the exception of global muscle weakness, central and peripheral neurological exam was otherwise normal. A non-contrast CT scan of his brain was reported as normal. Ferrous equipment prevented an MRI scan being performed. Metoclopramide, which he had been receiving to

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Table 1. Sequential whole blood Mn levels and liver function tests.

Days since starting PN	Whole blood Mn (nmol/l) (normal range 72.8–218.5 nmol/l)	Plasma Bilirubin (μmol/l) (<21 μmol/l)	Plasma ALT (IU/l) (normal range <50 IU/L)	Plasma ALP (IU/l) (normal range 30–130 IU/l)
80	429	16	25	539
103	404	22	18	347
157	428	14	38	501
199	261	13	58	497
226	288	10	64	674

improve gastrointestinal motility, was discontinued, but without any beneficial effect on the tremor.

Whole blood Mn was significantly increased at 429 nmol/L (reference range 72.8–218.5 nmol/l) at the time the tremors developed. In view of the possibility of Mn toxicity, Mn was withheld immediately from the PN regimen and has been withheld throughout the rest of the admission. Mn levels have remained elevated to date, as shown in Table 1. Also shown in Table 1 are the results of liver function tests measured at the time of the Mn sampling; alkaline phosphatase has been raised throughout admission. Urinary Mn excretion at five months was increased at 24.68 nmol/l (normal; less than 1 nmol/l). The symptoms have persisted to date, despite the removal of supplemental Mn from the PN preparation four months previously.

Discussion

Physiological role

Mn plays a role in a wide range of physiological functions. It is the cationic component incorporated into a number of metalloenzymes, which catalyze important reactions in the body. It is also required as a cofactor in other processes. Its name is thought to derive from the Greek word for 'magic', highlighting its diverse effects.

Mn is one of a number of cations able to combine with superoxide dismutase; Mn superoxide dismutase (MnSOD) reduces oxidative stress in the mitochondria through the catalytic conversion of superoxide radicals to hydrogen peroxide, which can be further reduced to water.

Mn participates in a number of metabolic processes. Arginase, for example, catalyses the conversion of L-arginine to L-ornithine, one of the steps in the urea cycle, the process for detoxifying ammonia. Pyruvate carboxylase is responsible for carbohydrate synthesis from pyruvate.

Mn is required for the formation of normal bone, cartilage, connective tissue and wound healing. Mn deficiency may cause poor development and accelerated loss of bone mass in later life.

Mn may also be involved in the normal functioning of the immune system, regulation of cellular energy, reproduction and digestion, and in maintaining coagulation homeostasis.

Pharmacokinetics

Approximately 10–20 mg of Mn is present in the average human body, of which 25–40% is present in bone.[1] Normally, less than 5% is absorbed from the gut.[1,2] Absorption is lower in men than in women.[3] Following absorption, Mn is transported to the liver; some is rapidly excreted into the bile, and the remainder enters the systemic circulation and is transported to the central nervous system and peripheral tissues. It is transported across cell membranes via the transferrin transport system (Mn^{3+}), and via the divalent metal transporter (DMT1), a Mn citrate transporter, a calcium ion channel and other mechanisms (Mn^{2+}), depending on the tissue and oxidation state of the ion.[4] Proportionately larger amounts of Mn are found in tissues rich in mitochondria (liver, kidney, pancreas) and rich in melanin (retina, pigmented skin).[5]

Mn in blood distributes very rapidly into other tissues, so that while elimination from the blood compartment is quick, less than 2 h in rats, terminal elimination is much slower.[6] Total body elimination in humans may be as long as 34 (females) to 48 (males) days,[3] and may be much longer from the brain.[7] Almost 90% of Mn excretion from the body is via the hepatobiliary system.

In contrast to the evidence for brain Mn influx, much less is known about Mn movement out of brain into blood. The brain efflux of manganese across the blood–brain barrier does not appear to occur through a transporter and is likely to occur slowly by diffusion. Hence, tissue deposition of Mn demonstrable by MRI and the Mn blood levels usually return to normal only after several months of cessation of exposure to Mn.[8] Mn appears to have an affinity for the extrapyramidal system. In rats chronically exposed to Mn, levels in the substantia nigra of the basal ganglia were found to be significantly higher than those found in the frontal cortex, striatum and hippocampus.[9]

Sources of manganese associated with toxicity

Enteric absorption is tightly regulated, and toxic levels from normal dietary absorption have not been reported. However, drinking water may contain excessive amounts, and several case reports describe deleterious cognitive and behavioural effects from drinking water.[10,11] There is concern that the current guidelines on the maximum safe limits in drinking water may be too high.[12]

The majority of reported cases of Mn toxicity relate to occupational exposure due to inhalation of airborne Mn by miners, welders and smelters.

There is also some concern about exposure from fuel additives such as methylcyclopentadienyl manganese tricarbonyl (MMT), used to improve the octane rating and as a lubricant. Combustion of MMT releases airborne Mn phosphate and sulphate from vehicle exhausts.

Mn toxicity has also been well described in individuals receiving PN.

Patients at risk from manganese accumulation and toxicity

Certain patient groups are more at risk of Mn accumulation than others. Neonates and children are more susceptible to Mn accumulation than adults; their intestinal absorption is higher, and biliary excretion is lower than in adults.[13] Formula milk may expose the neonate to excessive levels, much higher than in breast-fed infants, and infants who receive Mn-containing PN, higher levels still.[13]

Iron deficiency has been shown to increase the risk of Mn accumulation in the brain, which may be because iron deficiency increases the absorption of Mn, probably related to competition for transport via the DMT1 or transferrin transporter.[14]

Patients with liver disease are also at an increased risk. Mn is excreted almost exclusively in the bile and concentrations in blood increase in cholestatic liver disease.[15,16] However, Mn itself can cause cholestasis, compounding the problem.[17] Mn accumulates in the basal ganglia in patients with cirrhosis, but the accumulation decreases following liver transplantation. Chronic liver failure and Mn intoxication give very similar clinical and radiological abnormalities; recent work has suggested that some of the imaging and clinical abnormalities in liver dysfunction and hepatic encephalopathy are related to Mn accumulation.[18,19] The mechanism of hepatotoxicity is poorly understood; one experimental model suggests that Mn in combination with bilirubin increases intracellular cholesterol levels which adversely affect bile formation and flow.[17] In our patient, the alkaline phosphatase has been raised throughout the admission to date, which might have contributed to the Mn retention and toxicity.

Effects of Manganese toxicity

Neurological effects. Given its predilection for the extrapyramidal system, movement disorders are commonly reported in Mn toxicity. These often include tremor and gait disturbance, mimicking Parkinsonism. Confusion, headache and dizziness are also reported. A study of manganism in welders reported the incidence of symptoms as shown in Table 2.[7]

In severe cases, a characteristic gait called 'cock-walking' is seen, in which patients walk on their toes, leaning forward. Extrapyramidal effects have been reported to remain static, or deteriorate over the proceeding years, even without continuing exposure to Mn.[20,21] In follow-up of one patient over 14 years, most of the other effects originally reported, including muscle pain, anxiety and fatigue, had improved.[21]

Manganism differs in some respects from idiopathic Parkinson's disease. In Parkinson's disease, tremors usually begin on one side of the body, whereas in Mn toxicity, the tremors tend to be bilateral[22] as seen in the patient described in this report. The response to treatment is also different: dopamine agonists are less effective.

Studies suggest that high blood Mn and subclinical Mn deposition (demonstrable by MRI scan) are much more common than overt signs of neurotoxicity. Upwards of 50% of patients receiving long-term PN with standard Mn dosing develop high blood Mn but most are not neurotoxic.[23] A study of 11 patients treated with long-term PN observed that all had high blood Mn, at least twice that of untreated subjects and all had demonstrable Mn accumulation.[24] However, only one patient had Parkinsonian symptoms.

Other effects. Cardiac Mn accumulation is reported to cause depression of cardiac myocytes and an increase in coronary vascular resistance. Its relevance in clinical practice is unclear; effects may only occur at levels well above those seen in humans.[25]

Subfertility and an increased risk of foetal abnormalities have also been reported in Mn overexposure.[7]

Mechanism of manganese neurotoxicity

How Mn causes neurotoxicity is not yet completely defined. Animal studies have shown that Mn binds to dopaminergic receptors causing auto-oxidation of dopamine and the formation of local catecholamines and free radicals, which can interfere with dopamine transmission, and cause tissue destruction. Mn is actively transported into neuronal cells, particularly of the basal ganglia, where it accumulates in the mitochondria. ATP synthesis is disrupted probably contributing to oxidative stress and cytotoxicity.[26] Mn^{3+} is taken up by cells more efficiently than Mn^{2+}, but is a more powerful reducer, and is therefore more toxic.[26]

Table 2. Frequency of symptoms associated with manganese toxicity.[7]

Effects of manganese toxicity	Incidence
Headache and insomnia	88%
Exaggerated tendon reflexes	83%
Hyper-myotonia	75%
Memory loss	75%
Emotional instability	35%
Tremor	23%
Speech disturbances	6%
Festinating gait	3%

Manganese supplementation in PN

Current recommendations on Mn supplementation in PN have recently been revised downwards. ASPEN guidelines previously recommended that 60–100 μg be added daily to PN, while current guidelines recommend only 55 μg.[27] This recommendation was based on the finding that in patients receiving this dose, blood Mn remained normal and there was no MRI evidence of neural Mn accumulation.[28] However, MRI signal intensity increased at daily doses of 110 μg. Whilst the true daily parenteral Mn requirement may be even lower than 55 μg, this dose at least appears to be safe providing there are no risk factors for Mn accumulation or other sources of intake. Current ESPEN guidelines advise that most standard preparations provide 200–550 μg per day, but that this should be revised downwards in critically ill patients,[29] without specifying a dose. The options for providing Mn and other trace elements in PN are constrained by the formulation of the available MTE products. Currently, withholding supplemental Mn means withholding the MTE product altogether and adding the other trace elements individually to the regimen or delivering by separate infusions. This is costly and labour intensive. Undoubtedly, there is a need for a wider range of MTE products for use in PN. In particular, low Mn and Mn-free products would enable clinicians to comply with the current ASPEN recommendations. This would help avoid many of the problems with Mn accumulation currently encountered in patients receiving long-term PN. The National Institute for Health and Care Excellence advises that Mn levels be checked 3- to 6-monthly in patients receiving PN.[30] Biochemical monitoring of Mn is advisable in patients treated with PN for more than 30 days.[31,32]

Most case reports of Mn neurotoxicity in the context of PN have been in adult patients supplemented with more than 500 μg per day or children supplemented with more than 40 μg/kg per day.[32] In addition, the risk of toxicity is greater in patients treated with PN for periods longer than three months.[33] Both the dose and cumulative dose therefore appear to be important risk factors for the development of neurotoxicity. However, neurotoxicity has also been reported with short-term PN. Mn encephalopathy developed in a 22-year-old patient with acute pancreatitis after only two weeks on PN.[34]

However, just as in the normal healthy population, there are few reported cases of Mn deficiency during PN; to the authors' knowledge, there is only one published case report of Mn deficiency occurring with PN, in a child with short bowel syndrome.[35] The rarity of Mn deficiency may be because parenteral Mn requirements are extremely low and probably already met by Mn present as a contaminant in the regimen, even without additional supplementation.[23] Reported contamination ranges from 5 to 38 μg/L of PN.

Some authorities suggest that Mn should not be added to PN in critically ill patients. Other recently published advice following an examination of Mn levels in patients receiving PN advises that if the whole blood Mn level is increased, supplemental Mn should be withheld entirely and should not be re-administered unless the level returns to normal. It also advises that Mn should not be supplemented if the patient has liver disease with an elevated bilirubin.[36] The presence of Mn as a contaminant means that it is currently not possible to eliminate it entirely from PN. However, this may change when better purification techniques are developed.

Monitoring

Mn deposition can occur asymptomatically and in the presence of normal serum levels. There are currently no reliable biomarkers to evaluate Mn exposure. Serum levels are considered to be a poor indicator of Mn exposure; erythrocytes account for 60–80% of Mn in the blood, and their turnover is slower than other cellular components, so whole blood Mn concentration is probably a better indicator.[37] Whole blood Mn levels also correlate more accurately with MRI changes of brain deposition, than do serum levels.[16] It also changes in a dose-dependent manner. However, whole blood Mn has notable limitations as a test of Mn status. It does not correlate strictly with neurotoxicity and the optimum time for sampling in relation to PN infusion is unclear. Limited weight can be given to individual results because whole blood Mn is subject to high biological variation. Results can be artefactually high because of contamination of the specimen tube. Clinicians should liaise with their trace element laboratory to ensure that the available tubes and collection system are appropriate for use. Despite the limitations, it is advisable for clinicians to have a high index of suspicion for toxicity in any patient with hypermanganesaemia. Having experienced the described case, it is the authors' contention that whole blood Mn should be monitored at least monthly in critically ill patients receiving PN,

at least until low-dose Mn products become available, and hypermanganasaemia should be acted upon promptly by withholding supplemental Mn. In the event that Mn is withheld following an artefactually increased Mn, the risk of deficiency developing is negligible for the reasons given above.

Whilst Parkinsonian features should be readily apparent clinically, some symptoms occurring early in toxicity may be mild and non-specific and therefore overlooked (Table 2). It is possible that neurophysiological tests such as tests of co-ordination and response speed may have a role in monitoring in an effort to detect neurotoxicity at an early stage.[37]

Treatment

Removal of the source of exposure is important. Response to treatment is variable, but is often poor.

Levodopa appears to be less effective than in idiopathic Parkinson's disease. One small study reported that only 50% of the patients showed improvement, and that the response to treatment lessened after 2–3 years of treatment.[38]

Chelating agents were first introduced in the 1960s. Although chelation therapy with EDTA may increase Mn excretion in urine and decrease the whole blood Mn concentration, this may not translate to any significant improvement in clinical symptoms.[7]

There has been recent interest in the effects of p-aminosalicylic acid. Animal studies suggest that pre-treatment or treatment concurrent with Mn exposure reduced the neurotoxic effects of Mn.[39] The mechanism was presumed to be via its chelating effects. Case reports suggest that it may produce clinical benefit in humans.[40]

In our patient, a small dose of Clonazepam was advised by our neurology team, which had some, partial, success.

Conclusion

Hypermanganesemia and neurotoxicity can occur in patients on long-term PN therapy, especially if there is liver disease. Accumulation may be slow, and the development of neurotoxicity may be subtle and insidious. Due to its long half-life of elimination, high Mn levels may take months to return to normal.

However, biomarkers for Mn toxicity have not been established; whole blood Mn is a more accurate indicator of tissue levels than serum or plasma Mn, but may not accurately represent accumulation.

The maximum daily dose of intravenous Mn has not been established. However, recent recommendations advise a reduced daily dose and more frequent monitoring of Mn than compared with previously. Parenteral Mn should be used with caution, if at all, in patients with reduced biliary excretion, especially in cholestatic liver disease. The authors suggest that critically ill patients receiving PN have at least monthly monitoring of Mn in whole blood.

The results of treatment of Mn neurotoxicity may be disappointing, but aminosalicylic acid shows promise.

Consent

Published with the written consent of the patient.

Declaration of conflicting interests

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