Elevated whole-blood manganese levels in adult patients prescribed 'manganese free' home parenteral nutrition

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Transparency Declaration

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

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Abstract

Background: Manganese toxicity can occur as a complication of home parenteral nutrition (HPN).

Patients can present with Parkinson disease-like symptoms. Preparations of trace elements in parenteral nutrition generally provide amounts in excess of requirements. Our previous review observed 60% of adult HPN patients to have high whole-blood manganese levels. Multi-trace element solutions were subsequently removed from all HPN formulations in January 2015. The aim of this service evaluation was to determine whole-blood concentrations of manganese in adult patients receiving HPN at the same institution to establish whether levels are now maintained within the normal reference range.

Methods: A retrospective review of whole-blood manganese levels in all patients receiving HPN between January 2018 and January 2019 from one hospital site was carried out.

Results: 100 patients were included in the review (59 female and 41 male). Normal whole-blood manganese levels (73-219 nmol/L) were observed in 70% of patients and elevated levels (>219 nmol/L) in 30% of patients. In the patients with elevated levels, 57% hadn't received manganese supplementation for at least one year prior to manganese being measured. Markers of cholestasis were similar between the two groups.

Conclusions: Incidence of elevated whole-blood manganese concentrations in patients receiving home parenteral nutrition decreased from 60% to 30% upon discontinued use of a multi-trace element solution. Elevated levels remain a concern despite patients being prescribed 'manganese-free' parenteral nutrition. Patients receive this trace element in amounts adequate to meet requirements through contamination and dietary intake alone, suggesting additional parenteral supplementation of manganese is not required.

Introduction

Manganese (Mn), an essential trace element (TE), is a cofactor for metalloenzymes, involved in processes such as immune and reproductive function, detoxification of damaging free radicals and neuronal health.¹ Less than 5% of dietary Mn is absorbed and of that 90% is excreted through the biliary tract.² Elevated Mn concentrations have been documented in patients with cholestasis but also in those with normal liver function.³⁻⁵ Detected by T1-weighted magnetic resonance imaging (MRI), excess Mn has been shown to accumulate in the brain at the level of the basal ganglia and can lead to neurotoxicity, a condition referred to as manganism.⁶ This might present as a Parkinsonian-like illness.

Mn is typically provided as part of a commercially available pre-mixed multi-trace element (MTE) solution in all patients receiving parenteral nutrition (PN). Additional Mn exposure is known to occur as a result of contamination via PN additives,⁷ likely at a level to meet requirements.⁸ Recommended standard doses of Mn in PN for adults have been decreasing (Table 1).⁹⁻¹³

In 2014, a previous review at our institution observed 60% of HPN patients to have high whole-blood Mn levels.¹⁴ Practice was changed and multi-trace element solutions were subsequently removed from all HPN formulations in January 2015. Rather, the trace elements zinc, selenium, iron and copper were added individually. Prescribing restrictions within the hospital meant inpatient PN still contained a MTE solution with 275 µg of Mn in each PN formulation. The aim of this service evaluation was to determine whole-blood concentrations of Mn in adult patients treated with HPN at the same institution to establish whether levels are now maintained within the normal reference range (73-219 nmol/L).

Methods

Population demographics: A retrospective review of whole-blood Mn levels in 100 adult patients receiving home parenteral nutrition (HPN) between January 2018 and January 2019 from one centre was carried out. Patient demographics and parenteral nutrition (PN) data include age, gender, length of time on PN, number of PN infusions per week, Mn level, and Mn exposure. Exposure to Mn describes

the number of days exposed to the multi-trace element (MTE) preparation, Additrac (Fresenius Kabi, UK), in the 12 months prior to having Mn measured. Additrac contains 275 µg of Mn per 10ml ampoule.

Sampling: All samples were analysed in the Department of Blood Sciences at our hospital. Blood for Mn analysis was taken into navy blue top (trace element-free) tubes (BD Vacutainer). Blood for routine tests was taken into gold top serum separator tubes (BD Vacutainer). Mn in whole-blood was analysed by inductively-coupled plasma-mass spectrometry in standard mode.

Statistics: Patients were grouped into those with normal whole-blood Mn levels (73-219 nmol/L), or elevated levels (>219 nmol/L). Data were entered into Microsoft Excel 2016, MSO (16.0.4738.1000) 32-bit and statistical analysis performed using two sample t-tests assuming unequal variances. The two Mn groups were compared for length of time on HPN, number of HPN infusions per week, exposure to Additrac, and liver function tests. Statistical significance was defined by a *P*-value of <0.05.

Analysis was based on retrospective anonymised information taken from patient records with full regard to individual confidentiality. The project was registered on the Clinical Effectiveness Register as a service review, project number 8400.

Results

100 patients were included in the analysis. The patients ranged in age from 19 to 73 years (median 55.8 years). Of the included patients, 51% were from our previous study in 2014. Both cohorts of patients were similar in terms of indications for parenteral nutrition (PN) and PN requirements. In this cohort, normal whole-blood Mn levels (73-219 nmol/L) were observed in 70 (70%) patients and elevated levels (>219 nmol/L) were observed in 30 (30%) patients. This compares to 40% and 60% of patients in 2014, respectively (Figure 1). Within the elevated group, 3 (10%) patients had Mn levels that were considered

clinically very high (>400 nmol/L). Higher Mn levels were associated with less time on HPN, indicative of more inpatient days in the previous 12 months. No patients demonstrated a Mn level below the reference interval (<73 nmol/L). Full data, expressed as medians and range, and statistical *P*-values are shown in Table 2.

In the normal Mn group (73-219 nmol/L), 8/70 (11%) patients had received a MTE solution in the year prior to having Mn measured, median, 21 days, compared to 13/30 (43%) in the elevated Mn group (>219 nmol/L), median 40 days, (Figure 2). Conversely, there were 17/30 (57%) participants in the elevated Mn group that had not been exposed to Mn in the previous year. As part of the evaluation, Mn was measured in a subset of unused 'Mn free' home parenteral nutrition bags ($n=6$) to determine the concentration of Mn through contamination. Levels were found to be 80 nmol/L.

There were no statistically significant differences between the two Mn groups for the number of infusions of PN per week ($p=0.18$), bilirubin ($p=0.14$) or alkaline phosphatase ($p=0.38$).

Discussion

This is the largest review of whole-blood Mn levels in patients receiving home parenteral nutrition (HPN) to date. It could be argued that our current practice of withholding multi-trace element (MTE) solutions risks deficiency of chromium, molybdenum, iodine and fluoride as individual preparations of these trace elements (TE) are not widely available in the UK. However, ASPEN¹¹ and ESPEN¹³ do not provide recommendations for the routine addition of molybdenum or fluoride to PN because of the widespread contamination of these TE. Similarly, iodine and chromium are both present as contaminants. ESPEN do recommend the routine addition of these TE, however, we encourage all of our patients to maintain some oral intake, particularly dairy and milk products which are rich in iodine and chromium, respectively. There have been no concerns of deficiency of these TE in our cohort of patients, although levels have not specifically been measured due to lack of reliable tests available.

As expected, higher Mn levels were observed in patients who had been exposed to a MTE solution as an inpatient in the 12 months prior to having Mn measured. Patients receive this MTE solution during unplanned hospital admissions and whilst being established on parenteral nutrition (PN). Only upon discharge would they receive 'Mn-free' PN provided by the homecare company. This explains higher Mn levels in those patients who have been receiving HPN the least length of time.

There were 17 patients (57%) in the elevated Mn group who had not received a MTE solution in the 12 months prior to having Mn measured. There are three likely explanations for the elevated levels observed. It is well known that the ingredients of PN are contaminated with Mn. The subset of 'Mn free' HPN bags (n=6) that were subjected to lab analysis contained Mn levels of 80 nmol/L; levels consistent with previous reports.¹⁵⁻¹⁶

A second explanation could be in relation to altered liver function. Excess Mn is normally excreted via the biliary tract and previous studies have shown high levels to be associated with cholestasis.¹⁷⁻¹⁸ In our patients however, there were no statistically significant differences between the two groups for bilirubin or alkaline phosphatase levels. Another explanation is in relation to dietary intake. All of our patients are encouraged to maintain some dietary and fluid intake. Although oral intake data were not collected for the purpose of this review; it is worth highlighting that tea is commonly consumed in our patient group. Moreover, a standard mug of tea (250mL) contains on average 0.45-1.3 mg (450-1300 µg) of Mn.¹⁹

To prevent potential deficiencies of other TE, and to minimise future exposure to Mn for HPN patients, alternative MTE preparations containing 55µg of Mn have been sought. A key finding in this review, however, is that there were no patients within this cohort that were deficient in Mn (<73 nmol/L), despite Mn being completely withheld from PN in 79/100 (79%) patients over the previous year. It is therefore possible that we may continue to see elevated Mn levels at supplementation levels of 55 µg per day. Whole-blood Mn levels will continue to be measured in all HPN patients at six monthly

intervals. Data will be reviewed in 12 months time to establish whether our change in practice has been effective in reducing the currently observed elevated whole-blood Mn levels.

Limitations

A limitation of the present evaluation is in defining those patients exposed to Mn via a multi-trace element (MTE) solution in the previous twelve months. It is unclear how long whole-blood Mn levels take to normalise following exposure and is likely dependant on multiple factors. A duration of 5 to 9 months has been reported in some studies,²⁰⁻²¹ and therefore a 12-month period for re-assessment was deemed adequate.

Conclusion

Incidence of elevated whole-blood manganese concentrations in patients receiving home parenteral nutrition (HPN) decreased from 60% to 30% upon discontinued use of multi-trace element solutions. However, elevated levels are an ongoing concern and are being seen in patients receiving 'Mn-free' HPN. Patients are receiving this trace element in amounts adequate to meet requirements through contamination and dietary intake alone; suggesting additional parenteral supplementation of Mn is not required. Research is required to determine the relationship between high whole-blood Mn levels and any adverse clinical outcome.

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Table 1: Recommended parenteral Mn supplementation in adults. AMA = American Medical Association.

ASPEN = American Society for Parenteral and Enteral Nutrition. AuSPEN = Australasian Society for

Parenteral and Enteral Nutrition. ESPEN = European Society for Clinical Nutrition and Metabolism.

Source	Year	Mn dose (µg/day)
AMA	1979	150-800
ESPEN	2009	165-275
ASPEN	2012	55
AuSPEN	2014	55
ESPEN	2016	60-100

Table 2: Demographic and parenteral nutrition data. E-Mn = elevated manganese, F = female, GI = gastrointestinal, HPN = home parenteral nutrition, IBD = inflammatory bowel disease, M = male, N = number of patients. Data are expressed as medians and range. N-Mn = normal manganese, PN = parenteral nutrition, SB = small bowel

Demographics and Parenteral Nutrition Data	Normal -Mn (73-219 nmol/L)	Elevated -Mn (>220nmol/L)	Statistical significance
N = 100 (59F, 41M)	N = 70 (39F, 31M)	N = 30 (20F, 10M)	
Median age (range; years)	57.1 (19-83)	52.7 (20-71)	
Indications for HPN (n):			
IBD	18	13	
SB ischaemia	22	3	
GI dysmotility	12	1	
Other	18	13	
Median Mn level (range; nmol/L)	158.8 (76-219)	271.7 (222.6-482.8)	
N (%) patients exposed to inpatient Additrac in the previous 12 months	8 (11)	13 (43)	p <0.001

Median length of time on HPN (range; months)	47.5 (9-254)	30 (6-100)	P <0.001
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Figure 1. Comparison of blood Mn levels from 2014 to 2018

Abbreviations: n = number of patients

Figure 2. Effect of inpatient exposure to Additrac in the previous 12 months on Mn levels

Abbreviations: n = number of patients, MTE = multi-trace element