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Dosing and Monitoring of Trace Elements in Long-Term Home Parenteral Nutrition Patients

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Background: Trace elements (TEs) dosing and monitoring in home parenteral nutrition (PN) patients vary with their underlying conditions. *Methods*: This retrospective observational study evaluated parenteral TE dosing, serum TE concentrations and monitoring, and dose-concentration relationships between TE doses and serum TE concentrations in 26 adult and adolescent home PN patients. *Results*: There was a total of 40,493 PN days. Average parenteral zinc doses of 9.1 mg/d and 7.6 mg/d resulted in the majority of serum zinc concentrations (90%) within normal range in patients with and without short bowel syndrome (SBS), respectively. Selenium at about 70 mcg/d resulted in about 60% of serum selenium concentrations within normal range, with 38% of values below normal in patients with and without SBS alike. Copper at 1 mg/d resulted in 22.5% of serum copper concentrations above the normal range. The majority of serum manganese (94.6%) and chromium (96%) concentrations were elevated. Serum TE concentrations were infrequently monitored. Significant relationships existed between doses and serum concentrations for zinc ($P < .0001$), manganese ($P = .012$), and chromium ($P < .0001$) but not for selenium or copper. *Conclusions:* TE doses in home PN should be individualized and adjusted based on regular monitoring of TE status. In long-term home PN patients, higher zinc and selenium doses may be necessary to maintain their normal serum concentrations. Lower copper doses and restrictions of manganese and chromium supplementation may be needed to avoid their accumulation. Relationships between TE doses and serum TE concentrations vary for each TE and underlying clinical conditions. (*JPEN J Parenter Enteral Nutr*. 2011;35:**736-747**)

Keywords: trace elements; home parenteral nutrition

Clinical Relevancy Statement

Trace elements (TEs) including zinc, selenium, copper, manganese, and chromium are essential components of parenteral nutrition (PN). Guidelines are available for the daily trace element maintenance requirements and supplementation in PN, but these have not addressed the long term TE requirements for home PN patients. Study results show that a fixed dose of the parenteral multi-trace element product continues to be commonly used for home PN patients. This practice may contribute to excessive copper, manganese, and chromium loading and may provide less than optimal zinc and selenium intake. Furthermore, monitoring of TE status in home PN patients is infrequent and inconsistent. Therefore, parenteral TE supplementation in home PN should be individualized based on regular monitoring of TE status and considering the patient's underlying clinical conditions.

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Introduction

Home parenteral nutrition (PN) is a life-saving therapy for patients with intestinal failure. Trace elements (TEs), including zinc, selenium, copper, manganese, and chromium, are micronutrients that serve different physiologic functions and are routinely supplemented in PN. Although TEs are required in relatively small amounts, their exact requirements vary with the individual's nutrition status and clinical conditions. Guidelines for adult parenteral zinc, copper, manganese, and chromium requirements were first released in 1979 by the American Medical

Table 1. Parenteral Trace Element Daily Supplementation Guidelines and Commercial Multitrace-5 Concentrate Injection[a]

	Zinc, mg	Selenium, mcg	Copper, mg	Manganese, mg	Chromium, mcg
AMA (1979)[1]	2.5–4	—	0.5–1.5	0.15–0.8	10–15
New York Academy of Medicine and AMA (1984)[2]	2.5–4	50–60	0.3–0.5	0.4–0.8	10–20
A.S.P.E.N. (1998)[5]					
Adults	2.5–5	—	0.3–0.5	0.06–0.1	10–15
A.S.P.E.N. (2004)[6]					
Adults >40 kg	2.5–5	20–60	0.3–0.5	0.06–0.1	10–15
Adolescents >40 kg	2–5	40–60	0.2–0.5	0.04–0.1	5–15
Multitrace-5 Concentrate Injection[a] (1 mL)	5	60	1	0.5	10

AMA, American Medical Association; A.S.P.E.N., American Society of Parenteral and Enteral Nutrition.
[a]American Regent, Inc (Shirley, NY).

Association (AMA)[1] and updated by the New York Academy of Medicine and the AMA in 1984 (Table 1).[2] The AMA guidelines have been used as a reference by the US Food and Drug Administration (FDA) for the labeling of parenteral multi-TE products, which have become the standard for TE dosing in PN. Following reports of TE imbalances in PN patients who received parenteral TE supplements based on the AMA guidelines,[2-4] the American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) released different guidelines for daily TE maintenance requirements and supplementation in PN in 1998 that were later revised in 2004 with added selenium recommendations (Table 1).[5,6]

TE supplementation and dose adjustments in PN are generally guided by serum TE concentrations. However, clinical conditions that alter TE clearance diversely affect serum TE concentrations. For instance, malabsorption syndromes such as short bowel syndrome (SBS), high fluid output enterocutaneous fistulas, and chronic diarrhea result in substantial zinc and selenium losses, which necessitate supplementation with higher than the recommended maintenance doses that are found in the multi-TE products. Conversely, patients with decreased bile flow such as hepatic cholestasis may require lower copper and manganese supplementation to avoid their accumulation, as both TEs are mainly eliminated via the bile and may accumulate to toxic levels, especially manganese.[7-9] Furthermore, manganese and chromium are known contaminants of the parenteral products used in the making of PN and provide additional intake that exceeds the maintenance requirements.[10-12] Although TE supplements are relatively safe, identifying the exact TE requirements in PN is challenged by the poor correlation of serum TE concentrations with tissue TE stores and the presence of underlying clinical conditions that variably affect TE balance. The fixed-dose parenteral multi-TE formulation that is based on the old AMA guidelines continues to be used in PN despite its provision of excessive copper, manganese, and chromium. Furthermore, the effects of TE dosing based on the A.S.P.E.N. TE dosing guidelines on serum TE concentrations have not been tested in long-term home PN patients.

The primary objectives of this study were to evaluate parenteral TE dosing, serum TE concentrations, and the frequency of serum TE monitoring in patients who received long-term home PN. The secondary objectives were to explore the relationships between parenteral TE doses and their respective serum TE concentrations, compare the doses and serum concentrations of zinc and selenium in patients with and without SBS, and compare the doses and serum concentrations of copper and manganese in patients with and without cholestasis.

Methods

This was a retrospective observational study that evaluated parenteral TE dosing, serum TE concentrations, and the frequency of monitoring serum TE concentrations in adult and adolescent home PN patients. Parenteral TE doses in PN were compared to the A.S.P.E.N. TE dosing guidelines. Serum TE concentrations were compared to reference ranges. Furthermore, the study explored the relationships between TE doses and their serum concentrations. The study was approved by the institutional review board.

Patients

Adult and adolescent patients >40 kg and who received home PN for at least 1 year (365 days) between May 1, 2002, and April 30, 2007, through a home infusion provider affiliated with a large university health system were identified using the home infusion pharmacy electronic database. The body weight >40 kg was used to classify patients as adolescents or adults, in accordance with the A.S.P.E.N. parenteral TE dosing guidelines (Table 1).

Data were extracted from patients' medical records of the home infusion provider and the university health system. The medical records of identified patients were reviewed retrospectively beginning with their first day of PN available on the pharmacy records starting from June 20, 1995, and ending August 31, 2008. Collected data included patients' age, gender, and body weight; indication(s) for home PN; PN start and stop dates; PN administration dates and frequency; doses of zinc, selenium, copper, manganese, and chromium in each PN prescription; serum TE concentrations; serum creatinine; and direct bilirubin concentrations, which were used to define cholestasis as the time period between serum direct bilirubin concentrations ≥2 mg/dL until the next measured serum direct bilirubin concentration was <2 mg/dL.

Data Extraction and Collection

Data were extracted using a modified version of RapidMiner (YALE open-source software; Rapid-I GmbH, Dortmund, Germany). A subject-based relational data-mining procedure was used to search multiple electronic patient tables and charts. Data were manually entered into an Excel (Microsoft, Redmond, WA) spreadsheet in a highly abstracted form (eg, TE dose per PN administration day, frequency, start and stop dates) and then converted to average daily and weekly TE dose for the entire duration of PN therapy. Data were entered using a paired key variable-matching method (unique patient study ID and date). In instances of duplicate or multiple records of a key, the information was combined and replaced by the aggregate mean. Validation procedures, consisting of double checks of entries, ensured the accuracy of manually entered data.

Collection and Assays of TE Blood Samples

Appropriate techniques for collection and preparation of blood TE samples were followed to minimize exogenous trace metal contamination. Metal-free syringes and stainless steel phlebotomy needles were used for venipuncture. Blood samples were collected in specifically designed metal-free royal blue–top tubes with no additives. After centrifugation, serum aliquots were transferred into metal-free containers or plastic vials while avoiding transfer of the cellular components of blood. Serum TE concentrations were analyzed and reported from 2 different laboratories (Mayo Medical Laboratories and The University of Michigan Health System Laboratories). Serum zinc and copper samples were assayed using graphite furnace atomic absorption. Serum selenium, manganese, and chromium samples were assayed using inductively coupled plasma–mass spectrometry (ICP-MS).

Table 2. Descriptive Characteristics of Home Parenteral Nutrition (PN) Patients

	No. (%)
Gender	
Male	7 (27)
Female	19 (73)
Age, y, range	14–71.5
Weight, kg, range	40.2–132
Indications for home PN	
Short bowel syndrome	10 (38)
Enterocutaneous fistula(s)	4 (15)
Chronic pancreatitis	3 (11.5)
Crohn's disease	3 (11.5)
Gastroparesis	2 (8)
Small bowel amyloidosis	2 (8)
Familial pseudo-obstruction	1 (4)
Gastrointestinal dysmotility	1 (4)

Data Analysis

The appropriateness of parenteral TE dosing was evaluated based on comparisons with the 2004 A.S.P.E.N. parenteral TE supplementation guidelines (Table 1). TE doses were categorized as below, within, or above the A.S.P.E.N.'s supplementation range for each TE. Similarly, serum TE concentrations were classified as below, within, or above in comparison to the reference serum concentration ranges. Group comparisons were performed for zinc and selenium doses and serum TE concentrations, based on the presence or absence of SBS. Group comparisons were also performed for copper and manganese doses based on the presence or absence of cholestasis. Because chromium and manganese were omitted at times from PN, serum chromium and manganese concentrations were compared during the times when patients did or did not receive either TE. The frequency of measuring each serum TE per year (365 days) was calculated. Because PN was administered daily or intermittently, average weekly TE doses were used to assess the relationships between TE doses and serum TE concentrations.

Statistical Analysis

Parenteral TE doses and underlying clinical conditions (SBS and cholestasis) were the independent variables, and serum TE concentrations were the dependent variables. A linear mixed model was used for comparative analyses. A linear regression mixed model was used to predict the relationship between TE doses and serum TE concentrations. Negative binomial regression analysis was used to predict the frequency of measured serum TE concentrations. Statistical analyses were performed using SAS software (version 9.2; SAS Institute, Inc, Cary, NC).

Table 3. Daily Parenteral Trace Element Doses in Home Parenteral Nutrition

Trace Element	Mean Daily Trace Element Doses	Range	*P* Value[a]
Zinc	7.65 ± 0.74 mg	3–15	
SBS	9.12 ± 1.15 mg	5–15	.12
Non-SBS	6.73 ± 0.91 mg	3–15	
Selenium	69.14 ± 2.56 mcg	30–120	
SBS	70.12 ± 4.19 mcg	40–120	.76
Non-SBS	68.54 ± 3.31 mcg	30–100	
Copper	0.99 ± 0.03 mg	0–2	
Manganese	0.47 ± 0.10 mg	0–0.5	
Chromium	9.33 ± 0.42 mcg	0–20	

All mean values are reported as mean ± SEM. SBS, short bowel syndrome.
[a]*P* values are for the differences between SBS and non-SBS patients.

Table 4. Number of Daily Parenteral Trace Element Doses Below, Within, and Above Dosing Ranges in Comparison to A.S.P.E.N.'s Guidelines[6,a]

Trace Element	Below (%)	Within (%)	Above (%)
Zinc	0	26,872 (66.4)	13,621 (33.6)
Selenium	0	25,107 (62.0)	15,386 (38.0)
Copper	756 (1.8)	1101 (2.7)	38,636 (95.5)
Manganese	3018 (7.4)	0	37,475 (92.6)
Chromium	4560 (11.3)	35,287 (87.1)	646 (1.6)

A.S.P.E.N., American Society for Parenteral and Enteral Nutrition.
[a]Daily parenteral trace element supplementation in parenteral nutrition according to the guidelines by A.S.P.E.N. for adolescents (up to 18 years of age and >40 kg): zinc 2–5 mg, selenium 40–60 mcg, copper 0.2–0.5 mg, manganese 0.04–0.1 mg, and chromium 5–15 mcg; adults (>18 years of age and >40 kg): zinc 2.5–5 mg, selenium 20–60 mcg, copper 0.3–0.5 mg, manganese 0.06–0.1 mg, and chromium 10–15 mcg.

Results

Patient Characteristics (Table 2)

There was a total of 26 patients (24 adults and 2 adolescents), with 7 males (27%) and 19 females (73%). During the study period, patients' age ranged from 14–71.5 years, and their body weight ranged from 40.2–132 kg. The most common indications for home PN were SBS (n = 10; 38%), enterocutaneous fistula(s) (n = 4; 15%), chronic pancreatitis (n = 3; 11.5%), and Crohn's disease (n = 3; 11.5%). Five patients developed cholestasis intermittently during their course of PN therapy. No clinical signs or symptoms of TE deficiencies or toxicities were observed.

PN

The total cumulative number of home PN days was 40,493, including 28,957 days (71.5%) of PN as the only source of nutrition and 11,536 days (28.5%) of supplemental PN for patients who were also receiving oral and/or enteral nutrition (EN).

Parenteral TE Doses (Tables 3 and 4)

The most commonly used TE supplementation dose in PN was the 1-mL fixed dose of the multi-TE concentrate that combined all 5 trace elements (Table 1).

Zinc. The mean daily dose of zinc was 7.65 ± 0.74 mg. SBS patients received a higher zinc dose as compared to non-SBS patients, but the difference was not statistically significant (9.12 ± 1.15 vs 6.73 ± 0.91 mg, respectively; $P = .12$). In comparison to A.S.P.E.N.'s daily parenteral zinc supplementation guidelines, 26,872 (66.4%) doses were within and 13,621 (33.6%) doses were above the dosing ranges.

Selenium. The mean daily selenium dose was 69.14 ± 2.56 mcg. Selenium doses were not significantly different between SBS patients and non-SBS patients (70.12 ± 4.19 vs 68.54 ± 3.31 mcg, respectively; $P = .76$). In comparison to A.S.P.E.N.'s daily parenteral selenium supplementation guidelines, 25,107 (62%) doses were within and 15,386 (38%) doses were above the dosing ranges.

Table 5. Serum Trace Element Concentrations

Trace Element (No.)	Mean Serum Trace Element Concentrations	Range[a]	*P* Value[b]
Zinc (146)	0.95 ± 0.24 mcg/mL	0.6–1.5	
SBS (59)	0.99 ± 0.07 mcg/mL	0.85–1.13	.47
Non-SBS (87)	0.92 ± 0.06 mcg/mL	0.79–1.05	
Selenium (115)	101.0 ± 24.39 ng/mL	54.5–143.86	
SBS (47)	105.30 ± 7.94 ng/mL	90.05–121.60	.50
Non-SBS (68)	98.76 ± 6.96 ng/mL	84.93–112.59	
Copper (40)[c]	1.25 ± 0.20 mcg/mL	0.95–1.73	
Manganese (37)[c]	1.69 ± 0.40 ng/mL	0.90–2.30	
Chromium (50)	2.82 ± 1.91 ng/mL	0.51–6.85	

All mean values are reported as mean ± SD, except for SBS and non-SBS values, which are mean ± SEM. SBS, short bowel syndrome.

[a]Serum reference ranges: zinc 0.55–1.50 mcg/mL, selenium 95–165 ng/mL, copper 0.7–1.4 mcg/mL (males) and 0.7–1.6 mcg/mL (females), manganese 0.40–0.85 ng/mL, and chromium <0.3 ng/mL.

[b]*P* values are for the differences between SBS and non-SBS patients.

[c]No serum copper or manganese concentrations were obtained during periods of cholestasis.

Copper. The mean daily copper dose was 0.99 ± 0.03 mg and was mostly unchanged in the presence or absence of cholestasis. In comparison to A.S.P.E.N.'s daily parenteral copper supplementation guidelines, 756 (1.8%) doses were below, 1101 (2.7%) within, and 38,636 (95.5%) above the dosing ranges. Only 1 of the 5 patients who developed cholestasis during the course of PN therapy had copper supplementation intermittently withheld in PN.

Manganese. The mean daily manganese dose was 0.47 ± 0.10 mg and was mostly unchanged in the presence or absence of cholestasis. In comparison to A.S.P.E.N.'s daily parenteral manganese supplementation guidelines, 3018 (7.4%) doses were below and 37,475 (92.6%) doses were above the dosing ranges. Two of the 5 patients who developed cholestasis during the course of PN therapy had manganese supplementation intermittently withheld in their PN.

Chromium. The mean daily chromium dose was 9.33 ± 0.42 mcg. In comparison to A.S.P.E.N.'s daily parenteral chromium supplementation guidelines, 4560 (11.3%) doses were below, 35,287 (87.1%) within, and 646 (1.6%) above the dosing ranges. Eight patients had chromium supplementation withheld in their PN in response to elevated serum chromium concentrations.

Serum TE Concentrations (Tables 5–7)

Zinc. The mean serum zinc concentration was 0.95 ± 0.24 mcg/mL and did not differ significantly between SBS and non-SBS patients (0.99 ± 0.07 and 0.92 ± 0.06 mcg/mL, respectively; *P* = .47). Of 146 serum zinc concentrations measured, 59 (40.4%) were obtained from SBS patients and 87 (59.6%) from non-SBS patients (*P* = .87), and the overall majority (90.5%) of values were within the reference range.

Selenium. The mean serum selenium concentration was 101 ± 24.39 ng/mL and did not differ significantly between SBS and non-SBS patients (105.3 ± 7.94 and 98.76 ± 6.96 ng/mL, respectively; *P* = .5). Of 115 serum selenium concentrations measured, 47 (40.9%) were from SBS patients and 68 (59.1%) from non-SBS patients (*P* = .67), with overall 44 (38.2%) values below, 69 (60%) within, and 2 (1.8%) above the reference range.

Copper. The mean serum copper concentration was 1.25 ± 0.20 mcg/mL. Of 40 serum copper concentrations measured, 31 (77.5%) were within and 9 (22.5%) above the reference range. No serum copper concentrations were measured during periods of cholestasis.

Manganese. The mean serum manganese concentration was 1.69 ± 0.40 ng/mL. Of 37 serum manganese concentrations measured, the majority (94.6%) were above the reference range. No serum manganese concentrations were measured during periods of cholestasis. Serum manganese concentrations were higher when manganese was supplemented as compared to when it was not supplemented in PN (1.78 ± 0.15 vs 1.28 ± 0.28 ng/mL, respectively), although the difference was not statistically significant (*P* = .1).

Chromium. The mean serum chromium concentration was 2.82 ± 1.91 ng/mL. Of 50 serum chromium concentrations measured, the majority (96%) were above the

Table 6. Number of Serum Trace Element Concentrations Below, Within, and Above Reference Ranges[a]

Trace Element (No.)	Below (%)	Within (%)	Above (%)	*P* Value[b]
Zinc (146)	8 (5.5)	132 (90.5)	6 (4.0)	
SBS (59)	3 (5.0)	53 (90.0)	3 (5.0)	.87
Non-SBS (87)	5 (5.8)	79 (90.8)	3 (3.4)	
Selenium (115)	44 (38.2)	69 (60.0)	2 (1.8)	
SBS (47)	18 (38.3)	29 (61.7)	0	.67
Non-SBS (68)	26 (38.2)	40 (58.8)	2 (3.0)	
Copper (40)[c]	0	31 (77.5)	9 (22.5)	
Manganese (37)[c]	0	2 (5.4)	35 (94.6)	
Chromium (50)	0	2 (4.0)	48 (96.0)	

All mean values are reported as mean ± SD, except for SBS and non-SBS values, which are mean ± SEM. SBS, short bowel syndrome.

[a]Serum reference ranges: zinc 0.55–1.50 mcg/mL, selenium 95–165 ng/mL, copper 0.7–1.4 mcg/mL (males) and 0.7–1.6 mcg/mL (females), manganese 0.40–0.85 ng/mL, and chromium <0.3 ng/mL.

[b]*P* values refer to comparisons of the differences between the percentages of measured serum zinc and selenium in SBS and non-SBS patients.

[c]No serum copper or manganese concentrations were obtained during periods of cholestasis.

Table 7. Serum Manganese and Chromium Concentrations in Patients Who Received Supplemented or Nonsupplemented Parenteral Nutrition Formulations

Trace Element	Mean Serum Trace Element Concentrations, ng/mL[a]	*P* Value[b]
Manganese		
Supplemented	1.78 ± 0.15	.1
Nonsupplemented	1.28 ± 0.28	
Chromium		
Supplemented	3.18 ± 0.49	<.0001
Nonsupplemented	1.83 ± 0.52	

All mean values are reported as mean ± SEM.

[a]Serum reference ranges: manganese 0.40–0.85 ng/mL and chromium <0.3 ng/mL.

[b]*P* values refer to comparisons of the differences in serum trace element concentrations in patients receiving supplemented or nonsupplemented parenteral nutrition formulations.

Table 8. Measurement Frequency of Serum Trace Elements Concentrations

Trace Element	Mean Frequency of Serum Trace Element Measurement Per Year (Range)	*P* Value[a]
Zinc	1.21 ± 0.74 (0–2.38)	
SBS	1.45 ± 0.53 (0.56–2.13)	.25
Non-SBS	1.05 ± 0.82 (0–2.38)	
Selenium	0.98 ± 0.74 (0–2.36)	
SBS	0.88 ± 0.75 (0–2.10)	.35
Non-SBS	0.88 ± 0.75 (0–2.10)	
Copper	0.39 ± 0.59 (0–2.36)	
Manganese	0.41 ± 0.59 (0–1.89)	
Chromium	0.53 ± 0.69 (0–2.34)	

All mean values are reported as mean ± SEM. SBS, short bowel syndrome.

[a]*P* values are for the differences between SBS and non-SBS patients.

reference range. Serum chromium concentrations were significantly higher when chromium was supplemented as compared to when chromium supplementation was withheld in PN (3.18 ± 0.49 vs 1.83 ± 0.52 ng/mL, respectively; $P < .0001$).

Frequency of Monitoring Serum TE Concentrations (Table 8)

Serum TE concentrations were monitored at the discretion of prescribers and/or home care clinicians. They were measured at different time intervals during the course of PN therapy, and the timing and frequency of these measurements varied widely among patients. The average frequencies of annual monitoring of serum TE concentrations (average number of serum TE concentrations measured per year) were 1.21 ± 0.74 for zinc, 0.98 ± 0.74 for selenium, 0.39 ± 0.59 for copper, 0.41 ± 0.59 for manganese, and 0.53 ± 0.69 for chromium. Although serum zinc concentrations were measured more frequently in SBS as compared to non-SBS patients (1.45 ± 0.53 and 1.05 ± 0.82, respectively), the difference was not statistically significant ($P = .25$). Serum selenium measurements were measured at a similar rate (0.88 ± 0.75) in SBS and non-SBS patients.

Relationships Between TE Doses and Serum TE Concentrations

There was a significant relationship between overall zinc doses and serum zinc concentrations ($P < .0001$) and in patients with and without SBS ($P = .004$ and $P = .002$, respectively). Significant dose-concentration relationships were also found between supplemented TE doses and their corresponding serum concentrations for manganese ($P = .012$) and chromium ($P < .0001$). The relationship was not significant between overall selenium doses and serum selenium concentrations ($P = .51$) or between selenium doses and their serum concentrations in patients with and without SBS ($P = .75$ and $P = .56$, respectively). When the dose-concentration relationships were compared between SBS and non-SBS patients for zinc and selenium doses and their corresponding serum concentrations, the differences between the 2 groups were not significant for either TE ($P = .20$ and $P = .90$, respectively). The relationship between copper doses and serum copper concentrations was not significant ($P = .77$).

Discussion

The AMA parenteral TE supplementation guidelines have been historically used as the basis for adult TE supplementation in PN.[1,2] Following reports of TE imbalances with TE supplementation based on the AMA guidelines, the A.S.P.E.N. safe practice guidelines provided revised TE dosing requirements in PN.[6] However, the fixed dose of parenteral multi-TE products that were formulated based on the old AMA guidelines has continued to be used. Furthermore, the outcomes of A.S.P.E.N. parenteral TE dosing recommendations on serum TE concentrations remain to be tested.

Zinc

Zinc plays a role in a variety of enzymatic, metabolic, and immunologic functions.[13] Study results show that an average zinc dose of 7.6 mg/d in PN maintained normal serum zinc concentrations in the majority (90%) of cases. The zinc dose exceeded what is recommended in the literature and by the A.S.P.E.N. guidelines for 2.5–5 mg/d in adults without increased intestinal zinc losses.[6,14,15]However, the zinc dose in our study was similar to the suggested dose of 8 mg/d for home PN patients to achieve normal serum zinc concentrations.[16] SBS patients required a higher zinc dose of about 9 mg/d as compared to 6.7 mg/d for non-SBS patients. These doses maintained normal serum zinc concentrations in about 90% of cases. Zinc requirements are increased by about 12 mg/L of small intestinal fluid volume, and SBS patients may lose up to 3.6 mg zinc per kg of intestinal fluid.[14] Thus, similar to our study results, a parenteral zinc dose of 10 mg/d has been suggested for patients with high intestinal fluid losses.[15] Because intestinal fluid losses are not typically collected or quantified in home care patients, it was difficult to provide an estimate of intestinal zinc losses. There was a strong relationship between zinc doses and serum zinc concentrations. This relationship has also been reported in studies with oral zinc supplementation, whereby serum zinc concentrations showed a consistent and positive response when zinc intake exceeded 2–3 mg/d but reached a plateau when zinc intake exceeded 25–30 mg/d.[13] In our study, zinc doses ranged from 3–15 mg/d, which may explain the observed strong relationship between zinc doses and serum zinc concentrations within this dosing range. Overall, the frequency of measuring serum zinc concentrations was low at 1.21 measurements per year. Although serum zinc concentrations were measured about 1.4 times more frequently in SBS than in non-SBS patients, the difference was not significant. The relatively more frequent measurements of serum zinc concentrations in SBS patients may be related to clinicians' awareness of the higher risk of zinc deficiency in SBS patients and the need for more frequent monitoring.

Selenium

Selenium is a cofactor of the glutathione peroxidase enzyme, the major antioxidant in the body.[17] Although the average selenium dose of about 70 mcg/d exceeded the A.S.P.E.N. maintenance dosing guidelines, about 38% of serum selenium concentrations were below normal in SBS and non-SBS patients alike. Although a minimum selenium dose of 50 mcg/d and a usual dose of 60 mcg/d have been recommended in PN,[15,17] our data show that even a higher parenteral selenium dose of about 70 mcg/d achieved normal serum selenium concentrations in only about 60% of cases. Higher maintenance selenium doses of 60–100 mcg/d have been actually suggested for adult home PN patients, and patients with selenium depletion may require even higher doses.[18] Selenium deficiency has been reported in SBS patients due to increased selenium losses in intestinal fluids.[19] In a study of non-SBS home PN patients, daily parenteral selenium doses of 63 mcg resulted in a wide range of serum selenium concentrations of 17.5–131 ng/mL, with 16% of values below normal levels.[16] In another study of home PN patients that included 5 patients with SBS, parenteral selenium 80 mcg/d followed by 160 mcg/d increased but did not consistently normalize serum selenium concentrations.[20] Higher selenium doses up to 250–400 mcg/d have been suggested to correct severe selenium deficiencies.[15,21] Therefore, higher selenium doses than what is recommended by the A.S.P.E.N. guidelines for parenteral selenium supplementation are needed to maintain normal serum selenium concentrations for the majority of home PN patients, especially when high selenium losses occur.

There was no significant relationship between selenium doses and serum selenium concentrations in SBS and non-SBS patients. Although in a prior study, plasma selenium concentrations increased with increasing selenium doses, there was no correlation between selenium doses and plasma selenium concentrations.[20] After initial gradual increase of serum selenium concentrations, selenium doses of 200 mcg/d for 3 months or 100 mcg/d for 8 months resulted in no significant change in serum selenium concentrations.[21] This might be explained by the observation that a correlation exists between selenium intake and serum selenium concentrations up to 70 ng/mL, above which a plateau is formed.[19] The plateau effect might explain our study results that found no relationship between selenium doses and serum selenium concentrations. Overall, the frequency of measuring serum selenium concentrations was low at 0.98 measurements per year and was similar in SBS and non-SBS patients. Plasma or serum selenium concentrations are most used to assess selenium status, but their usefulness for monitoring the changes in selenium intake has been questioned as they reflect acute selenium distribution between tissues rather than selenium stores.[17,18] The erythrocyte glutathione peroxidase activity may better reflect long-term selenium status, although it is not commonly used in clinical practice. The role of platelet and plasma glutathione peroxidase activity as indicators of selenium status is debatable.[17,20,21]

Copper

Copper plays a role in hematopoiesis, connective tissue synthesis, and oxidative enzymes.[17] Study results show that the average daily copper dose far exceeded A.S.P.E.N.'s guidelines, and most (95.5%) of the doses were above the recommended dosing range. Serum copper concentrations were maintained within the normal range in 77.5% of cases, with the remaining serum concentrations above normal levels. In a similar study of home PN patients, copper 1 mg/d resulted initially in serum copper concentrations of 1.35 + 0.25 mcg/mL, then increased to 1.79 + 0.33 mcg/mL after 6 months of copper supplementation, with serum copper concentrations frequently above the reference range.[22] When a lower copper dose of 0.13 mg/d was in home PN, serum copper concentrations varied widely from 0.5–3.17 mcg/L, with 62.5% of values within, 34.3% below, and 3.2% above normal.[16] In comparison to the latter study, our study results show that a 7.6-fold higher copper dose (0.99 mg/d) resulted in 22.5% of serum copper concentrations above normal. As such, copper dosing based on A.S.P.E.N.'s guidelines for copper supplementation in PN represents an intermediate dosing between the lower copper doses used[16] and the higher AMA dosing guidelines.[1] In addition to standard copper supplementation in PN, copper contaminants in PN solutions may provide additional copper loading as much as 2-fold higher than recommended for copper supplementation.[23] Because copper is primarily eliminated via the bile, its excretion is decreased in patients with reduced bile flow such as cholestasis. Although copper may accumulate in patients with cholestasis, caution is needed when copper supplementation is restricted. Copper deficiency has been reported within 6 weeks to 15 months after copper was omitted from the PN of patients with cholestasis, resulting in pancytopenia and fatalities.[24-27] Although copper toxicity has not been reported in PN patients, hepatic copper accumulation may still occur.[28] Autopsies of SBS patients who received copper doses of 1.4 mg/d in their home PN showed copper accumulation in the liver and kidneys, especially in patients who died of liver failure.[3] This raises the concern for potential subclinical copper toxicity that may occur in home PN patients, especially when higher doses are used. Because there is no simple way to clinically measure bile flow, it is difficult to estimate the amount of copper elimination in the bile. It is also difficult to predict the duration of copper supplementation that predisposes to copper accumulation, and hepatic copper loading does not correlate with the duration of copper supplementation in home PN.[28] In our study, serum copper concentrations were not measured during cholestasis, and copper doses were likely adjusted empirically based on clinicians' experience whenever serum bilirubin concentrations became elevated. The average frequency of serum copper concentrations measurements was low at 0.39 per year. Although serum copper concentrations do not accurately reflect copper accumulation, it is prudent to regularly measure serum copper concentrations in long-term PN patients. Copper supplementation should be conservative in patients with cholestasis with regular monitoring of copper status to avoid deficiency.[15,28] The relationship between copper doses and serum copper concentrations was not significant. Because serum copper concentrations were not measured during cholestasis, we could not compare this relationship between patients with and without cholestasis.

Manganese

Manganese is a component of metalloenzymes and is associated with oxidative phosphorylation and mucopolysaccharide metabolism.[17,29] The majority (92.6%) of manganese doses far exceeded the upper limit of A.S.P.E.N. supplementation guidelines. The average serum manganese concentration was about 2-fold higher than the upper end of the serum manganese reference range. An average manganese dose of 0.47 mg/d resulted in about 95% of serum manganese concentrations above normal. In 1 study, a lower manganese dose of 0.28 mg/d in PN resulted in about 97% of serum manganese concentrations above

the normal range.[16] Patients who received manganese in their PN had 1.4-fold higher serum manganese concentrations as compared to those who did not receive manganese supplementation. Serum manganese concentrations remained elevated even after manganese was omitted from PN. One patient without cholestasis had elevated serum manganese concentrations after 349 days of manganese removal from PN. This might be explained by the manganese contaminants of parenteral products that are used in the making of PN. Manganese contaminants in PN can be as high as 0.31 mg/L, with dextrose and electrolyte solutions contributing as much as 0.038 mg/L.[6,10,30-32] Home PN patients have had elevated serum manganese concentrations after more than 10 years of eliminating manganese from their PN.[33] Because manganese is mostly excreted in the bile, manganese accumulation occurs in patients with cholestasis. Manganese deposits in the basal ganglia, causing neurological toxicity, have been shown on magnetic resonance imaging (MRI) of home PN patients with elevated serum manganese concentrations. Manganese loading may also cause liver toxicity and cholestasis.[34,35] Manganese doses were not consistently reduced and no serum manganese concentrations were measured during cholestasis. We found a significant relationship between manganese doses and serum manganese concentrations. This is similar to the results of another study that showed a relationship between manganese supplementation in PN and whole-blood manganese concentrations in patients who received home PN for up to 226 months.[36] However, this is in contrast to another study that showed no association between manganese doses and serum and whole-blood manganese concentrations.[33] Although serum manganese concentrations are frequently used to assess manganese status in PN patients, whole-blood manganese concentrations are believed to be more representative of manganese status.[37] The frequency of measuring serum manganese concentrations was only at 0.41 measurements per year. This was a low rate of monitoring considering the risk of manganese accumulation in long-term PN patients.[9]

Chromium

Chromium is a cofactor for insulin function that enhances insulin effects to improve glucose metabolism through the glucose tolerance factor.[38] In comparison to A.S.P.E.N.'s guidelines, the majority (87.1%) of chromium doses were within the dosing range. However, the vast majority (96%) of serum chromium concentrations far exceeded the reference range. Patients who received chromium in their PN had significantly 1.73-fold higher serum chromium concentrations as compared to those who received no chromium supplementation. Serum chromium concentrations remained elevated even when chromium was not supplemented. In 2 patients, serum chromium concentrations remained elevated after receiving chromium-free PN for 1.3 and 2 years, respectively. These findings may reflect excess chromium intake from chromium contaminants. None of the patients had decreased renal function during the study, which rules out any chromium accumulation secondary to acute or chronic kidney injury. Chromium contamination in PN is well documented and varies between manufacturers and product lots.[12,39-43] Chromium contaminants in parenteral products may contribute up to 100% more of chromium intake,[43] causing up to a 40-fold increase in serum chromium concentrations and substantially higher tissue chromium accumulation.[40] In our study, serum chromium concentrations reached about 23-fold (6.85 ng/mL) the upper reference range (0.3 ng/mL). This is similar to reported data of serum chromium concentrations exceeding 21 times the upper level of normal.[40] Although chromium toxicity in PN patients has not been reported, there are concerns of possible association between high serum chromium concentrations and decreased kidney function in children.[43] To the contrary, glucose intolerance and neuropathy were linked to chromium deficiency in early studies of home PN patients.[44-46] In long-term PN patients, supplemental chromium may not be necessary, and chromium supplementation based on A.S.P.E.N.'s guidelines may be excessive, considering the significance of chromium contamination of PN solutions. Serum chromium concentrations were measured at a low frequency of 0.53 measurements per year. Considering the extent of chromium contamination, serum chromium concentrations should be measured more frequently at shorter intervals in home PN patients.[39] Although serum chromium concentrations are the most widely used to monitor chromium status in PN patients, no correlation was found between serum chromium and tissue chromium stores.[47] However, we found a strong relationship between chromium doses and serum chromium concentrations. The interpretation of this relationship is difficult considering the unknown but possibly significant amounts of chromium contaminants in PN solutions that may have affected serum chromium concentrations.

Summary

The FDA-labeled adult parenteral multi-TE formulation that is available in the United States is based on the outdated AMA recommendations and indirectly encourages the use of the fixed-dose multi-TE product that does not accurately meet the TE requirements for home PN patients. Although the parenteral multi-TE product provides the convenience of providing all TEs in one dose, a fixed dose may not fit individual TE requirements for long-term PN

patients. The A.S.P.E.N. guidelines for daily TE supplementation in PN formulations represent approximations of standard TE intakes in the healthy population and assume normal losses and age-related organ function. Interindividual variations for TE requirements may exist, and intakes can best be achieved by using individualized TE products.[6] In comparison to the A.S.P.E.N. guidelines for maintenance TE supplementation in PN, our study results show that long-term home PN patients >40 kg may require higher zinc and selenium doses to maintain their serum concentrations within the normal range, especially when high intestinal losses occur. Lower copper and manganese doses are needed especially in the setting of cholestasis. Lower manganese and chromium doses are required to avoid accumulation, especially when PN contaminants are considered. These can only be achieved by individualizing TE supplementation based on regular monitoring of TE status and according to underlying clinical conditions.

The frequency of monitoring TE status in long-term home PN has not been well documented and has been mostly dependent on clinicians' practice experiences. Our study results show infrequent and random monitoring of serum TE concentrations in long-term home PN patients. Therefore, guidelines and standards for regular monitoring of TE status should be implemented to improve the safety and efficacy of PN therapy. Although it may not be possible to completely eliminate TE contaminants from parenteral products, the FDA should consider requiring manufacturers to specify the maximum safe or allowable TE contamination limits in parenteral products, similar to the case of aluminum.[48]

The relationship between parenteral TE doses and serum TE concentrations in PN patients has not been explored sufficiently because of complex TE kinetics related to tissue distribution and elimination and the variability of underlying conditions that affect TE balance. In our study, the dose-concentration relationships between TE doses and serum TE concentrations were significant for zinc, manganese, and chromium but were less predictable for selenium and copper. The clinical significance of these relationships requires further evaluation.

Study Limitations

The study findings emphasize the importance of accurately dosing and monitoring TE status in home PN patients but present with some limitations, especially those inherent to a retrospective observational study design. Data collected were based on the assumption that any prescribed home PN was administered to the patient, although no actual home PN administration records were available to confirm the actual PN infusions. Furthermore, we assumed that total TE doses were delivered to patients, although PN storage and temperature can significantly decrease zinc, copper, and manganese availability in home PN solutions that are typically compounded and delivered in batches of 7–10 days for home supply.[49] Because serum direct bilirubin concentrations were not measured at regular intervals and we did not consider the clinical signs and symptoms in the diagnosis of cholestasis, it was therefore difficult to ascertain the exact duration of cholestasis. Also, other TE sources such as PN contaminants, diet, EN, or oral supplements, were not considered, which may have influenced the results. Of note, dose-concentration relationships do not constitute pharmacokinetic models to predict serum TE concentrations in relation to TE doses, and serum TE concentrations do not determine the chemical form of a particular element, biologic activity, or availability in the body as a whole and may not represent actual body stores.[50-52] Serum TE concentrations do not necessarily reflect total body TE stores, and levels are affected by the response to stress or injury. Although tissue TE redistribution occurs during the phase of the inflammatory response to stress, this is typically significant in acutely ill or hospitalized patients[53] and is of a lesser significance in stable home PN patients. Because inflammatory markers (eg, serum C-reactive protein or CRP levels) are not routinely measured in the home setting, we could not assess the level of the inflammatory process and its possible effects on serum TE concentrations. When zinc and selenium supplementation and their serum concentrations were compared between SBS and non-SBS patients, the non-SBS population included patients with malabsorption disorders who may have also had intestinal TE losses. However, SBS patients have exceedingly high intestinal zinc and selenium losses due to short intestinal surface absorption area, rapid gastrointestinal transit time, and chronic diarrhea. Last, we could not locate any documentation of clinical signs and symptoms of TE deficiencies or toxicities, and thus we cannot speculate on the clinical consequences of low or high serum TE concentrations.

Another limitation is related to possible manganese and chromium needle contamination during blood sampling. This is of particular interest given the observed high serum chromium and manganese concentrations when neither TE was deliberately supplemented in PN. Chromium and manganese are known to leach from metal needles.[54,55] However, contamination control was followed during specimen sampling and collection by using metal-free syringes and special metal-free TE blood collection tubes. The magnitude of steel needle contamination risk is likely minimal when the contact time between the needle and blood sample is kept at a minimum, which is the typical technique followed during blood sampling and collection.[56]

Conclusions

Parenteral TE dosing should be individualized for home PN patients rather than using a fixed-dose multi-TE product. TE dose adjustments should be guided by regular monitoring of TE status. Higher than maintenance zinc and selenium doses may be required to maintain normal serum zinc and selenium concentrations in long-term home PN patients, especially under conditions of increased intestinal losses. Lower copper doses may be necessary to avoid long term copper accumulation. Excessive manganese and chromium loading occurs in long-term PN patients, and restriction of manganese and chromium supplementation may be required to avoid their accumulation. The dose-concentration relationships between TE doses and serum concentrations vary with each TE and underlying clinical conditions.

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