Carol Rees Parrish, R.D., MS, Series Editor

Trace Element Monitoring and Therapy for Adult Patients Receiving Long-term Total Parenteral Nutrition

Theresa A. Fessler

Thousands of patients in this country rely on long-term total parenteral nutrition (PN) for survival, because of severe impairment of gastrointestinal (GI) function. Parenteral nutrition provides a limited range of nutrients and bypasses GI homeostatic mechanisms leaving patients at risk for deficiencies and toxicities, including trace elements. Literature on trace elements for PN patients is limited; the majority being case reports, thus provision of optimal care is challenging. Trace element mixtures used today have been designed consistent with guidelines issued over 25 years ago. The objective of this article is to provide practical up-to-date guidelines for trace element monitoring and therapy for adult long-term PN patients based on the limited data available. This article discusses likelihood of deficiencies and toxicities, dosages, monitoring frequencies, and laboratory tests for the essential trace elements: manganese, selenium, zinc, chromium, copper, iron, molybdenum and iodine, as well as aluminum, a harmful contaminant.

INTRODUCTION

An estimated 40,000 people in the United States rely on long-term parenteral nutrition (PN) (1). In order to effectively monitor and treat trace element status for PN patients, one must be aware of requirements, excretion routes, the risks and manifestations of deficiencies and toxicities, available parenteral products, and the reliability of laboratory tests.

Nearly twenty trace elements are thought to be essential for humans (2) but only five are commonly added to PN. The numerous and complex metabolic

Theresa A. Fessler MS, RD, CNSD, Nutrition Support Specialist, University of Virginia Health System, Digestive Health Center of Excellence, Charlottesville, VA.

(continued on page 51)

(continued from page 44)

Table 1
Daily Parenteral Trace Element Supplementation for Adults

Trace Element	*Previous Recommendations (AMA-1979)*	*Recent Recommendations (ASPEN-2004)*	*Daily dose—using current trace element products (in Table 2 below) in amounts of 1,2 or 5 mL, to approximate requirements*
Manganese	150–800 mcg	60–100 mcg	200, 500, or 800 mcg
Selenium	(none)	20–60 mcg	0, or 40, or 60 mcg
Zinc	2.5–4.0 mg	2.5–5 mg	2–5 mg
Chromium	10–15 mcg	10–15 mcg	8–10 mcg
Copper	0.5–1.5 mg	0.3–0.5 mg	0.8–1 mg

functions of the essential trace elements are discussed elsewhere (2–6). Commercially available parenteral trace element additives provide a mixture of four or five trace elements; either chromium (Cr), copper (Cu), manganese (Mn), and zinc (Zn); or, these four elements plus selenium (Se). (Tables 1 and 2). Current trace element mixtures, formulated by 1979 guidelines (7), provide two to eight times the recent recommended requirement of Mn, and twice the requirement of Cu in a daily dose that otherwise meets the requirements for the remaining trace elements (8). (Tables 1 and 2). All five elements, as well as Molybdenum (Mb) and Iodine (I) can be purchased as single-element additives. Iron (Fe) solutions are available for separate IV infusion (Table 3).

MANGANESE (Mn)

Many long-term PN patients develop elevations of whole blood, plasma or serum, and red blood cell manganese without toxicity symptoms (9–14). Hypermanganesemia is more likely to develop in cholestatic patients, as the primary route of excretion is in bile, yet it has also been reported in PN patients with normal liver function (2,11,13–15). Mn contamination of PN solutions is approximately 10–38 mcg per 2 L (11,16). Hypermanganesemia may be due to the excessive Mn provided by current combination trace element additives, as well as contamination of PN (Tables 1 and 2). An optimal dose for Mn in PN may be as low as 55 micrograms (mcg) per day (12).

Table 2
Combination Parenteral Trace Element Products for Adults

Drug name	*Volume (mL)*	*Chromium (mcg)*	*Copper (mg)*	*Manganese (mcg)*	*Zinc (mg)*	*Selenium (mcg)*
Multitrace-4[a]	1	4	0.4	100	1	0
4 Trace Elements Injection[b]	5	10	1	800	4	0
Multitrace-4 Concentrate[a]	1	10	1	500	5	0
Multitrace-5[a]	1	4	0.4	100	1	20
Multitrace-5 Concentrate[a]	1	10	1	500	5	60

Single trace elements are also available for Cr, Cu, Mn, Zn[a,b], Se[a,c], and Mb[a,c] and I[c]
[a]American Regent (www.americanregent.com)
[b]Hospira (www.hospira.com)
[c]American Pharmaceutical Partners (www.appdrugs.com)

Table 3
Parenteral Iron Products

Product	*Adult IV Dosage and Administration* (mg of elemental iron)*	*Maximum daily dose (mg of elemental iron)*	*Drug name Manufacturer and Website*
Iron dextran	Test dose of 0.5 mL (25 mg) followed by 1 hour observation[a]	Undiluted: 2 mL (100 mg)[a]	InFeD, Watson Pharma, Inc. www.watsonpharma.com
	Undiluted: 1mL/min, (≤50 mg/min)[a], or 500–1000 mg diluted in 250–1000 mL normal saline over 4–6 hours[b]		DexFerrum, American Regent Inc. www.americanregent.com
Iron sucrose	Undiluted: 1mL/min (20 mg/min), over 5 minutes, or 5 mL (100 mg) diluted in 100 mL 0.9% NaCl infused over 15 min[a]	5 mL (100 mg) 1–3 times per Week[a]	Venofer American Regent, Inc. www.americanregent.com
Sodium ferric gluconate	Undiluted: 1 mL/min (12.5 mg/min), or 10 mL (125 mg) diluted in 100 mL 0.9% NaCl infused over 1 hour[a]	10 mL (125 mg)[a]	Ferrlecit Watson Pharma, Inc. www.watsonpharma.com

*Do not mix with other medications or parenteral nutrition solutions
[a] Drug Facts & Comparisons, Physician's desk reference, and Manufacturer information
[b] Kumpf (36)

There are no known accounts of Mn deficiency in PN patients. Symptomatic Mn toxicity while on PN has been reported in several cases, with Parkinson-like symptoms such as tremor and gait disturbance; and/or confusion, headache, and dizziness (17–21). Mn toxicity is associated with increased signal intensity in the globus pallidus of the basal ganglia on brain magnetic resonance images (MRI) and has historically been reported in patients with liver disease or in cases of environmental Mn exposure (15). Increased MRI signal intensity has also been found in hypermanganesemic PN patients, some with, and some without neurologic symptoms, and some with and some without cholestasis (10,11,17–21). The intensity of brain MRI declines after five months or more of discontinuation of Mn supplementation (10), and, based on limited data, toxicity symptoms should alleviate within a period ranging from several days to several months (17,19,21).

Whole blood Mn can elevate and decline within three months of provision and withdrawal of Mn supplementation (10). Whole blood Mn is a more accurate indicator of tissue levels than serum or plasma Mn (9,10,12). Erythrocyte Mn may be the most accurate indicator of tissue concentrations (11), but it is not available, or routine, at most medical labs, while the whole blood Mn test is more widely available.

SELENIUM (Se)

Se deficiency is well documented in patients on long-term PN without added Se. In a review of literature, Yusef found eight cases of cardiomyopathy and six cases of skeletal myopathy reported from 1979–1998 caused by deficiency of Se in patients on PN (22). Clinical deficiency has been found after three months to two years or longer (4,22,23). In a recent case, cardiomyopathy and undetectable blood Se was reported in a man after receiving PN for three months with no added Se (22). The patient's clinical symptoms of congestive heart failure subsided and echocardiograph showed normal ventricle size after receiving 150 mcg of Se per day for several weeks. In another recent report, a woman with Crohn's disease on long-term PN had whitened nail beds, muscle weakness, and macrocytosis along with undetectable plasma Se. Her symptoms reversed after several weeks of supplementation with Se, although plasma Se did not change (23).

(continued on page 54)

(continued from page 52)

Selenium toxicity has been known to occur in areas of high Se soil content (6), but has not been reported in PN patients. Selenium contamination in PN is relatively low, with approximately 21 micrograms per 2 L (16). Se excretion is primarily in urine (5). Some Se may also be lost in intestinal secretions (2).

Plasma or serum glutathione peroxidase activity is correlated with plasma or serum Se; both are good indicators to rule out Se *deficiency* (6,24–26). However the activities of these enzymes are not accurate in ruling out toxicity, as they do not continue to increase with additional Se intake after nutrition requirements are met (6). Erythrocyte Se and erythrocyte glutathione peroxidase activity are indicators of current Se status (24,26), but can stay within normal range up to three and six months respectively, while patients are deficient in Se intake. (26). Serum or plasma Se declines more quickly than does erythrocyte Se, thus are better indicators of recent Se intake or deficiency (24,26). For patients who have had small bowel resection, inflammatory bowel disease or other intestinal disorders, Se levels should be checked prior to starting PN, and every three months if deficiency is found, as they are likely to be depleted in Se due to poor nutrient absorption (24,25).

ZINC (Zn)

Zn deficiency has been reported in patients on PN without added Zn, with subsequent alleviation of symptoms after Zn supplementation (4). Zn deficiency symptoms include impaired taste and smell, skin lesions, alopecia, glossitis, stomatitis, mental depression, diarrhea and depressed immune function. (2–4). Skin lesions can occur after six months of PN without added Zn (4). Zinc deficiency is more common in patients with increased losses from pancreatic or intestinal fluids, which are main routes of Zn excretion, thus patients may be Zn deficient prior to starting PN (4,27). Wolman, et al measured the amount of Zn in stool and ostomy output, and studied Zn balance in patients on PN with no oral intake. Zn balance was achieved with only 3 mg/day of supplemental Zn in patients without excessive stool or ostomy output. Wolman estimated that positive Zn balance could be achieved by the addition of 17 mg Zn per Kg of ileostomy or stool output in patients with intact small bowel, and 12 mg Zn per Kg of fluid secreted from a proximal small bowel fistula or duodeno- or jejunocolostomy (27). Based on the Wolman study, the addition of higher amounts of Zn in PN for patients with consistent excessive losses of GI fluids has been recommended. At UVAHS, we typically add only 5–15 mg of Zn in addition to the maintenance amount of 5 mg per day and have not seen deficiency symptoms.

Zn toxicity in PN patients with appropriate Zn content has not been reported. Zn toxicity associated with elevated blood amylase levels after inadvertent Zn overdose in PN has been reported in one study of 7 patients (28). The total parenteral Zn intake in that study was estimated at approximately 50–75 mg per day (28). Zn contamination in PN is small, approximately, 1.1 mg per 2 L (16). Serum or plasma Zn levels are not good indicators of Zn status, as the majority of body Zn is in muscle, skeleton, and liver (4,29). During septic episodes, plasma Zn will be low as it is sequestered by the liver. It will also be low in patients with hypoalbuminemia, as it is primarily bound to albumin and alpha-2 macroglobulin in the blood (2).

CHROMIUM (Cr)

Three cases of Cr deficiency have been reported in patients on PN without added Cr (4,30). Symptoms included insulin resistance, hyperglycemia, neuropathy, and encephalopathy. Cr deficiency symptoms have been found after as little as five months and up to three years on PN, and were corrected with Cr supplementation (4,30).

Trivalent Cr, the nutritionally relevant form, is present as a significant contaminant in PN solutions, primarily from amino acid solutions and phosphate salts. Lipids may also contribute, depending upon the manufacturer and amount used (30,31). PN solutions have been reported to contain contaminant Cr in amounts of 15 mcg per 2 L, and as 2.4–8.1 mcg per day. (16,30).

Elevated serum Cr levels have been reported in PN patients, but there are no known reports of Cr toxicity symptoms (4,25,30,31). In one case, serum Cr was elevated to >20 times normal after one year of PN in an adult patient with normal renal function (25). Leung reported elevated serum Cr in 94% of their hospitalized

(continued on page 56)

(continued from page 54)

Table 4
University of Virginia Health System
Trace Element Monitoring Guidelines for Long-Term PN

Trace Element	*Baseline (if appropriate)*	*3 months*	*6 to 12 months (if deficiency or toxicity suspected)*	*Lab Test*
Manganese	X (t bili ≥3.5)	X*		Whole Blood
Selenium	X (excess GI loss)		X	serum
Zinc	X (excess GI loss)		X	serum
Chromium			?	serum
Copper		X (tbili ≥3.5		serum
Ferritin	X	X		serum
Iron**		X (if ferritin low)		serum

*Check Manganese every month if total bilirubin >3.5.
**Hgb and Hct are monitored every 1–4 weeks.
Used with permission from the University of Virginia Health System Nutrition Support Traineeship Syllabus (49).

PN patients, 50% of which had levels over ten times normal (31). Since Cr is excreted in the urine (4,5), it makes sense that patients with renal failure may require restriction of parenteral Cr intake, and monitoring, yet there is no clear evidence to support this practice.

Plasma and serum Cr are not ideal clinical indicators of Cr status. Normal Cr levels are measured in very small amounts, near detection limits, and contamination of samples can alter results (2,5). Because of contaminant Cr, daily addition of Cr in PN might not be needed, but is still recommended until there is more evidence that contaminant amounts consistently meet requirements (3, 30). Additional studies are needed to determine a reliable clinical indicator of Cr status, the effects of prolonged elevated blood Cr levels and how much Cr should be supplemented in PN. (2,3,5,30).

COPPER (Cu)

Copper toxicity resulting in liver damage has been reported in patients with Wilson's disease and other genetic disorders of copper metabolism, and in one person who consumed large amounts of oral Cu (5), but it has not been reported in PN patients (4). Even so, some practitioners avoid the use of Cu in patients with cholestatic liver disease, as toxicity is a potential risk. About 80% of parenteral Cu is excreted in bile and 20% in urine (4). Cu contamination in PN is minimal; approximately 82 micrograms (0.082 mg) per 2 L (16). Based on limited data, it is reasonable to decrease the amount of Cu in PN for cholestatic patients, and monitor for Cu deficiency in patients with prolonged excessive GI losses. Shike, et al estimated parenteral Cu needs to be 0.3 mg per day for patients without excessive stool or GI output, 0.4–0.5 mg/d if GI secretions are greater than 300 g/d, and as low as 0.15 mg/d for patients with liver dysfunction (32). It is worth noting that current combination trace element additives contain over twice the requirement of Cu (Tables 1 and 2).

Copper deficiency in PN patients has been documented in at least 14 case reports, with deficiency apparent after one to 30 months of PN (33). Both serum Cu and ceruloplasmin levels decline, and symptoms include leukopenia, neutropenia, hypochromic anemia that is not responsive to iron supplementation, and in some cases, thrombocytopenia (4,32–34). According to two recent case reports, in which Cu was removed from PN because of significant cholestasis (t bili 10.9 and 19.0), severe Cu deficiency symptoms can occur within 2–15 months (33,34). Based on these two recent cases, symptom improvement and normalization of Cu levels can be expected after one to six weeks of Cu supplementation (33,34).

Serum copper is 60–95% bound to ceruloplasmin (5). Both serum Cu and ceruloplasmin are reliable indi-

(continued on page 58)

(continued from page 56)

Table 5
Trace Element Deficiency and Toxicity Symptoms in Adults (2,5,6,32,48)

Trace Element	*Deficiency*	*Toxicity*
Manganese	Impaired metabolism of carbohydrate and lipid, dermatitis, impaired protein synthesis, weight loss. (has not been reported in PN patients).	Extrapyramidal neurologic symptoms: headache, tremor, facial nerve deficit, gait disturbance. Hyperintensity of signals on brain magnetic resonance images in basal ganglia.
Selenium	Cardiomyopathy, skeletal myopathy, myalgias, myositis, impaired cellular immunity, discoloration of nails.	Alopecia, brittle hair and nails, skin rash, GI disturbance, "garlic" breath odor, nervous system abnormalities.
Zinc	Dermatitis, alopecia, anorexia, reduced taste sensitivity, impaired immune function, impaired wound healing, glucose intolerance.	Anemia, hyperamylasemia, fever, central nervous system dysfunction in renal patients; deficiency of Cu (*enteral* Zn interferes with Cu absorption).
Chromium	Glucose intolerance, hyperlipidemia, peripheral neuropathy, encephalopathy	No known toxicity of Cr^{3+} (trivalent form). Has not been reported in PN patients.
Copper	Hypochromic, microcytic anemia, leukopenia, neutropenia, skeletal abnormalities, and rarely, thrombocytopenia.	Accumulation in liver, hepatocellular damage.
Iron	Hypochromic microcytic anemia, pallor, fatigue, decreased work performance.	Hemosiderosis, hemochromatosis, accumulation in liver and heart, some endocrine tissues; iron toxicity can be fatal.
Molybdenum	Tachycardia, tachypnea, headache, night blindness, lethargy.	Limited toxicity data for humans. Possible gout (high incidence in areas where soil is high in Mo), and possible excessive urinary copper excretion.
Iodine	Hypothyroidism – weakness, cold intolerance, weight gain, thinning hair, goiter (thyroid enlargement).	Thyroiditis, goiter, hypo- or hyperthyroidism, thyroid papillary cancer, dermatoses (iodermia).

cators of Cu deficiency, but not so for toxicity. Supplementation with Cu above requirements should not increase serum Cu or ceruloplasmin (5), however, when copper is elevated in cholestatic patients, it is typically removed from PN solutions and monitored, as the main route of copper excretion is in bile. As an acute phase reactant, ceruloplasmin will increase with liver disease, malignancy, inflammatory states, and infection, so elevation in ceruloplasmin or serum Cu does not necessarily rule out deficiency (4,5). Serum Cu may be more reliable than ceruloplasmin for detecting deficiency (34).

IRON (Fe)

Fe deficiency has been reported in long-term PN patients after only two months, yet some patients do not show signs of deficiency for up to a year or longer (35). Menstruating women, and patients with blood loss (wounds, GI bleeding, lab draws), will be more prone to developing Fe deficiency. A typical home patient will get labs drawn every week at a "cost" of ~10–20 mL of blood.

(continued on page 60)

(continued from page 58)

Iron is not a routine additive in PN solutions for several reasons. Body stores of iron are generally sufficient if PN is needed for less than six months (3,4). Iron dextran, the most commonly used form of parenteral Fe in the United States, has been associated with life-threatening anaphylactic reactions, with actual risk estimated at 0.6–0.7% (36). Trivalent iron (iron dextran) can cause lipid emulsions to destabilize and separate, thus it cannot be used in "3 in 1" solutions, commonly used in home care (8,37). Parenteral iron can potentially lead to iron toxicity, as it bypasses the primary mechanism for homeostasis (the intestinal mucosa) (36). Parenteral iron should not be used in patients with infection, as it may promote growth of bacteria and compromise host immune function (36).

Any PN dependent patient with a functional stomach and duodenum can be treated with oral or enteral iron. Efforts should be taken to enhance iron absorption by having the patient take it with a vitamin C source, and at the same time, avoid inhibitors of absorption such as tea, bran, and foods that contain phytates (cereals, nuts, legumes). Taking iron in small doses along with food—if the patient can tolerate, will help to minimize a possible side effect of nausea. The ferrous form of iron is more readily absorbed. In this author's experience, serum ferritin levels have been maintained within normal range for over a year in PN dependent patients who tolerated small amounts of oral nutrition; one without, and three with, the use of oral iron supplements.

Intravenous iron, available as iron-dextran, iron-sucrose, or sodium ferric gluconate, can be administered in one or more doses if the patient does not respond to oral iron therapy (Table 3) (36,38). For patients with iron deficiency anemia, the Fe replacement dose in milligrams can be calculated (36):

$0.3 \times \text{Wt} \times (100 - [\text{actual Hgb} \times 100/\text{desired Hgb}])$
Wt in pounds. Hgb in g/dL

Iron dextran can be added to non-lipid containing PN in small amounts of 10 mg per day temporarily; or 10 mg per week, or 25–50 mg per month for maintenance, but is actually not recommended by the manufacturers of IV iron products (8,35,36,39). There is no data to determine if iron sucrose or sodium ferric gluconate can be added to PN solutions, and manufacturers do not recommend it (8, 39).

Serum ferritin levels can be used to evaluate deficiency, but because ferritin levels rise in patients with malignancy, infection and other inflammatory conditions, a high ferritin level does not always indicate adequate iron stores (36).

MOLYBDENUM (Mo) AND IODINE (I)

Molybdenum (Mo) and Iodine (I) are not routinely supplemented in long-term PN, and parenteral requirements have not been established (4). The daily *oral* requirements are 45 mcg of Mo, and 150 mcg of I (5). Iodine deficiency would be expected to produce symptoms of hypothyroidism (2), and has not been reported in adult PN patients (4). Mo deficiency, as evidenced by biochemical abnormalities including elevated plasma methionine and low serum uric acid has been reported in one patient after 12 months of PN (40). Blood Mo levels were not measured. The patient had defects in sulfur amino acid metabolism, and in the breakdown of purines and pyrimidines; reactions that are catalyzed by the Mo-containing enzymes, sulfite and xanthine oxidase. (40,41). Symptoms included tachycardia, tachypnea, headache, nausea, vomiting, vision problems and coma. Symptoms subsided and biochemical abnormalities improved after treatment with 300 mcg ammonium molybdate per day (40). Because deficiency of Mo and I are rare or nonexistent in adult PN patients, it is likely that they may be present as contaminants in PN solutions (4). Toxicity of Mo and I in PN patients has not been reported. Little is known about the usefulness of plasma or serum Mo measurements as a marker of Mo status (5).

ALUMINUM (Al)

Aluminum is an undesired contaminant of all components of PN solutions, measured in one study as 428 mcg per 2L, but with variable content depending on manufacturer and batch (16,42,43). Parenteral Al has been implicated in the development of metabolic bone disease, neurologic disease, encephalopathy in dialysis patients, cholestasis, and microcytic anemia. Because parenteral Al is excreted in urine, Al toxicity is more likely in patients with impaired renal function, and in neonates, yet all patients on PN may be at risk

(continued on page 63)

(continued from page 60)

Table 6
Considerations for Monitoring Selected Trace Elements in Patients on Long-Term PN

Manganese (Mn)
- Check whole blood Mn every 3 months, and every month for those with total bilirubin >3.5. Use erythrocyte Mn if the test is available.
- If whole blood Mn levels are elevated, or if Mn toxicity symptoms are present, remove Mn by adding trace elements as individual components.
- If Mn levels decline below normal, resume use of a standard combination trace element additive, or use separate trace element components and only 60–100 mcg of Mn per day.

Selenium (Se)
- Use Se supplementation for any patient who requires PN. Find out if your hospital or home infusion provider uses a trace element solution that contains Se (some may use a standard additive without Se).
- Check serum Se if deficiency is suspected or is being treated.

Zinc (Zn)
- Check serum Zn if deficiency is suspected or being treated; be aware that serum levels are not sensitive indicators of Zn status.
- An additional 5–15 mg Zn per day may be added for patients with consistent excessive GI losses.

Chromium (Cr)
- Consider smaller doses of Cr and checking serum Cr levels for patients with renal failure.
- If Cr has been excluded from PN, monitor for signs of deficiency.

Copper (Cu)
- Check serum Cu if deficiency or toxicity is suspected, and every 3 months for patients with elevated total bilirubin.
- If serum Cu levels are elevated in patients with cholestasis, decrease or temporarily omit Cu from PN.
- If Cu has been excluded from PN, recheck Cu levels monthly, while observing for signs of deficiency.
- Be aware that Cu levels can be elevated with ceruloplasmin in certain conditions, so it does not always detect deficiency or toxicity.

Iron (Fe)
- Check serum ferritin levels every 3 months and monitor for deficiency symptoms.
- Serum ferritin levels rise in patients with malignancy, infection and other inflammatory conditions, thus a high ferritin level does not always indicate adequate iron stores.
- Rule out other conditions, such as anemia of chronic disease, or deficiencies of copper or vitamin B_{12}.
- For iron deficient patients in whom oral Fe therapy is ineffective, provide IV iron in an infusion clinic.
- If iron dextran is used, give a 25 mg test dose (0.5 mL) followed by a period of one hour of observation for anaphylactic reactions prior to administering the intended replacement dose; and if a reaction occurs, use a different Fe source.
- Administration of IV iron is not recommended during infection.

Molybdenum (Mo) and Iodone (I)
- Consider checking serum or plasma Mo levels if deficiency symptoms are identified, but note that reliability of this test is not proven. Other biochemical abnormalities such as elevated plasma methionine may be more indicative of Mo deficiency.
- If iodine deficiency is suspected, evaluate thyroid function.
- If deficiency symptoms are identified, supplementation of Mo or I may be indicated.

Aluminum (Al)
- Make an effort to limit Al content of formulas by use of current Al content labeling, and use of sodium phosphate instead of potassium phosphate salts.
- Although calcium chloride is lower in Al than is calcium gluconate, it is not recommended, as Ca chloride will increase risk of Ca phosphate precipitation in PN.

Used with permission from the University of Virginia Health System Nutrition Support Traineeship Syllabus (49).

(25,43,44). In one case, a 74-year-old man with normal renal function had elevated plasma Al within two weeks of starting PN, and further increases during the next six months (25).

In full PN admixtures, the highest contributors of Al are calcium gluconate and phosphate salts. Amino acid solutions, although relatively low in contaminant Al, are significant sources because of the larger volume used in the final solution. (42,43). Besides being present in all of the component materials used in PN, Al leaches out of glass containers in which parenteral solutions are autoclaved and stored (45,46).

The Food and Drug Administration (FDA) has recently mandated a warning statement and labeling requirements for parenteral products, which took effect July 2004. The warning on parenteral solution labels states that Al intake greater than 4–5 mcg/Kg per day for patients with impaired kidney function or premature neonates can cause accumulation of Al associated with central nervous system and bone toxicity. Al content must be listed on labels for small volume (≤100 mL) parenteral products, and a limit of 25 mcg Al per L is specified for large volume (≥100 mL) parenteral solutions (44).

CONSIDERATIONS FOR TRACE ELEMENT MONITORING

Periodic physical examinations should include evaluation for symptoms of trace element toxicities or deficiencies. Home health nurses, patients, and caregivers can be helpful in identification of abnormal symptoms, and in estimating amounts of ostomy, fistula or stool output in the home setting. Questions of this type should be asked during visits and telephone calls.

To avoid contamination, special tube and stopper types are needed for some of the trace element tests, and use of powder-free gloves may be required when drawing blood (47). Different labs will have different specifications for each test. Check with your laboratory, and place instructions with the orders to prevent waste. Write clearly and legibly to avoid misunderstanding. Nurses, phlebotomists, and even laboratory personnel may be unfamiliar with trace elements. We have had to reorder whole blood manganese several times because repeat magnesium tests were done. To help assure that correct procedures are followed to maintain test validity, specimens for trace element tests can be drawn in a laboratory or clinic when possible. Some trace element tests will be sent out to other labs, so it may take two weeks or longer to receive results.

SUMMARY

The available literature on trace element nutrition has lead to the development of guidelines for monitoring and treatment for long-term adult patients who rely on PN. Practical guidelines for monitoring and therapy for each trace element are listed in Table 6. These guidelines are based on the limited literature available and clinical experience. Information about products, parenteral requirements and dosages, the risks and symptoms of deficiencies and toxicities, and the usefulness of laboratory tests can help to optimize care for patients who rely on long-term PN. ■

References

1. DeLegge MH. Demographics of Home Parenteral Nutrition. *J Parenter Enteral Nutr,* 2002; 26(Suppl):S60-S62.
2. Baumgartner TG. Trace elements in clinical nutrition. *Nutr Clin Pract,* 1993;8:251-263.
3. Leung FY. Trace elements in parenteral micronutrition. *Clin Biochem,* 1995;28:561-566.
4. Frankel DA. Supplementation of trace elements in parenteral nutrition: rationale and recommendations. *Nutrition Research,* 1993;13:583-596.
5. Food and Nutrition Board, Institute of Medicine—National Academy of Sciences. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc.* c. 2001 National Academy Press, Washington DC.
6. Food and Nutrition Board, Institute of Medicine-National Academy of Sciences. Selenium (Chapter 7) In: *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids.* c. 2000. National Academy Press, Washington DC, pp. 284-324.
7. American Medical Association Department of Foods and Nutrition: Guidelines for essential trace element preparations for parenteral use. A statement by an expert panel. *J Amer Med Assoc,* 1979;241:2051-2054.
8. Task Force for the Revision of Safe Practices for Parenteral Nutrition. Mirtallo J, Canada T, Johnson D, et al. Safe practices for parenteral nutrition. *J Parenter Enteral Nutr,* 2004; 28:S39-S70.
9. Wardle CA, Forbes A, Roberts NB, Jawhari AV, Shenkin A. Hypermanganesemia in long-term intravenous nutrition and chronic liver disease. *J Parenter Enteral Nutr,* 1999; 23:350-355.
10. Takagi Y, Okada A, Sando K, et al. On-off study of manganese administration to adult patients undergoing home parenteral nutrition: new indices of in vivo manganese level. *J Parenter Enteral Nutr,* 2001;25:87-92.
11. Bertinet DB, Tinivella M, Balzola FA, et al. Brain manganese deposition and blood levels in patients undergoing home parenteral nutrition. *J Parenter Enteral Nutr,* 2000;24:223-227.

12. Takagi Y, Okada A, Sando K, et al. Evaluation of indexes of in vivo manganese status and the optimal intravenous dose for adult patients undergoing home parenteral nutrition. *Am J Clin Nutr,* 2002;75:112-118.
13. Siepler JK, Nishikawa A, Diamantidis T, Okamoto R. Asymptomatic hypermanganesemia in long-term home parenteral nutrition patients. *Nutr Clin Pract,* 2003;18:370-373.
14. Fitzgerald K, Mikalunas V, Rubin H, et al. Hypermanganesemia in patients receiving total parenteral nutrition. *J Parenter Enteral Nutr,* 1999;23:333-336.
15. Lucchini R, Albini E, Placidi D, et al. Brain magnetic resonance imaging and manganese exposure. *NeuroToxicol,* 2000;21:769-775.
16. Pluhator-Murton MM, Fedorak RN, Audette RJ, et al. Trace element contamination of total parenteral nutrition. 1. Contribution of component solutions. *J Parenter Enteral Nutr,* 1999;23:222-227.
17. Masumoto K, Suita S, Taguchi T, et al. Manganese intoxication during intermittent parenteral nutrition: report of two cases. *J Parenter Enteral Nutr,* 2001; 25: 95-99.
18. Nagatomo S, Umehara F, Hanada K, et al. Manganese intoxication during total parenteral nutrition: report of two cases and review of the literature. *J Neurological Sciences,* 1999;162:102-105.
19. O'Donnell K, Radigan A. Hypermanganesemia in an acute care setting. *Nutr Clin Pract,* 2003;18:374-376.
20. Fredstrom S, Rogosheske J, Gupta P, Burns LJ. Case report: Extrapyramidal symptoms in a BMT recipient with hyperintense basal ganglia and elevated manganese. *Bone Marrow Transplantation,* 1995;15:989-992.
21. Alves G, Thiebot J, Tracqui A, et al. Neurologic disorders due to brain manganese deposition in a jaundiced patient receiving long-term parenteral nutrition. *J Parenter Enteral Nutr,* 1997;21:41-45.
22. Yusuf SW, Rehman Q, Casscells W. Cardiomyopathy in association with selenium deficiency: a case report. *J Parenter Enteral Nutr,* 2002; 26:63-66.
23. Ishida T, Himeno K, Torigoe Y, et al. Selenium deficiency in a patient with Crohn's disease receiving long-term total parenteral nutrition. *Intern Med,* 2003;42:154-157.
24. Rannem T, Ladefoged K, Hylander E, et al. Selenium depletion in patients with gastrointestinal diseases: are there any predictive factors. *Scand J Gastroenterol,* 1998; 33:1057-1061.
25. Leung FY, Grace DM, Alfieri MAH, Bradley C. Abnormal trace elements in a patient on total parenteral nutrition with normal renal function. *Clin Biochem,* 1995; 28:297-302.
26. Hatanaka N, Nakaden H, Yamamoto Y, et al. Selenium kinetics and changes in glutathione peroxidase activities in patients receiving long-term parenteral nutrition and effects of supplementation with selenite. *Nutrition,* 2000;16:22-26.
27. Wolman SL, Anderson GH, Marliss EB, et al. Zinc in total parenteral nutrition: requirements and metabolic effects. *Gastroenterology,* 1979;76:458-467.
28. Faintuch J, Faintuch JJ, Toledo M, et al. Hyperamylasemia associated with zinc overdose during parenteral nutrition. *J Parenter Enteral Nutr,* 1978;2:640-645.
29. Baumgartner T. Parenteral Micronutrition (Chapter 1) In: *Clinical Guide to Parenteral Micronutrition,* Third edition. Fujisawa, USA, Inc. 1997:8-16.
30. Ito Y, Alcock NW, Shils ME. Chromium content of total parenteral nutrition solutions. *J Parenter Enteral Nutr,* 1990;14:610-614.
31. Leung FY, Galbraith LV. Elevated serum chromium in patients on total parenteral nutrition and the ionic species of contaminant chromium. *Biol Trace Elem Res,* 1995: 50:221-228.
32. Shike M, Roulet M, Kurian R, et al. Copper metabolism and requirements in total parenteral nutrition. *Gastroenterol,* 1981; 81:290-297.
33. Fuhrman MP, Herrmann V, Masidonski P, Eby C. Pancytopenia after removal of copper from total parenteral nutrition. *J Parenter Enteral Nutr,* 2000;24:361-366.
34. Spiegel JE, Willenbucher F. Rapid development of severe copper deficiency in a patient with Crohn's disease receiving parenteral nutrition. *J Parenter Enteral Nutr,* 1999;23:169-172.
35. Khaodhiar L, Keane-Ellison M, Tawa NE, et al. Iron deficiency anemia in patients receiving home total parenteral nutrition. *J Parenter Enteral Nutr,* 2002; 26:114-119.
36. Kumpf VJ. Update on parenteral iron therapy. *Nutr Clin Pract,* 2003;18:318-326.
37. Driscoll DF, Bhargava HN, Li L, et al. Physiochemical stability of total nutrient admixtures. *Am J Hosp Pharm,* 1995;52:623-634.
38. Yee J, Besarab A. Iron sucrose: the oldest iron therapy becomes new. *Am J Kidney Dis,* 2002;40:1111-1121.
39. Physicians' Desk Reference. For: Venofer Injection, American Regent, Inc. Rev. 2003; INFeD Injection and Ferrlecit Injection, Watson Pharma, Inc.2001.
40. Abumrad NN, Schneider AJ, Steel D, et al. Amino acid intolerance during prolonged total parenteral nutrition therapy. *Am J Clin Nutr,* 1981;34:2551-2559.
41. Sardesai VM. Molybdenum: An essential trace element. *Nutr Clin Pract,* 1993;8:277-281.
42. Driscoll DF. Aluminum contamination and total parenteral nutrition admixtures. Newslines publication of AAI Pharma 2003;9: 1-4.
43. Davis A, Spillane R, Zublena L. Aluminum: a problem trace metal in nutrition support. *Nutr Clin Prac,* 1999;14:227-231.
44. Federal Aluminum Mandate: What you need to know. *Newsflash* Published by Mayne Pharma 2004;2:1-3.
45. Bohrer D, do Nascimento PC, Binotto R, et al. Influence of the glass packing on the contamination of pharmaceutical products by aluminum. Part II: amino acids for parenteral nutrition. *J Trace Elem Med Biol,* 2001;15:103-108.
46. Frey OR, Maier L. In a letter to the editor: Polyethylene vials of calcium gluconate reduce aluminum contamination of TPN. *Annals of Pharmacotherapy,* 2000;34:811-812.
47. Quest Diagnostics Website: *www.questdiagnostics.com*
48. Jensen GL, Binkley J. Clinical manifestations of nutrient deficiency. *J Parenter Enteral Nutr,* 2002;26: Supplement S 29-S33.
49. Fessler T. Trace elements in long term TPN. In: Parrish CR, Krenitsky J, McCray S. *University of Virginia Health System Nutrition Support Traineeship Syllabus.* Available through the University of Virginia Health System Nutrition Services, Charlottesville, VA, January 2003. For more information, E-mail Linda Niven at: ltn6m@virginia.edu.