

Micronutrient Status in Patients Receiving Home Parenteral Nutrition

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Date accepted: 24 March 1997

ABSTRACT

Administration of home parenteral nutrition (HPN) to patients with intestinal failure requires attention to caloric content of feeds, fluid, electrolyte balance, and micronutrient status. Peripheral blood estimations of vitamins and trace elements may be abnormal, but their clinical significance in relation to deficiency or toxicity states is not always clear. We sought to determine the incidence and nature of clinical micronutrient abnormality in our HPN program. Clinical assessment and case record review of 49 patients actively receiving HPN was undertaken, and, in 32 of these patients, serum micronutrient levels were assayed. Clinical evidence of micronutrient deficiency was identified in 16 patients (33%). Iron deficiency anemia occurred in 14 patients which resolved after iron supplementation in all except 1 patient who had persistent intestinal blood loss. Anemia was precipitated in six patients by identifiable clinical events (acute gastrointestinal disease in five and menorrhagia in one), and in two others folate deficiency coexisted. Biotin deficiency developed in three patients, manifested by dry eyes and angular cheilitis or hair loss. Vitamin A deficiency resulting in visual disturbance developed in one patient who was not receiving multivitamin supplements at that time. Serum levels of zinc, copper, selenium, manganese, vitamin A, and vitamin E were measured in 32 patients. No patient had normal levels of all six micronutrients. Nevertheless, there was no clinical evidence of toxicity or deficiency in any of these patients at the time assays were performed. In conclusion, abnormalities of micronutrient status are common in HPN patients, but serious sequelae appear to be unusual. *Nutrition* 1997;13:941-944. ©Elsevier Science Inc. 1997

Key words: home parenteral nutrition, micronutrient, vitamin, trace element

INTRODUCTION

Patients receiving home parenteral nutrition (HPN) for intestinal failure have complex needs. Special attention to the underlying disease process and psychosocial problems, in addition to the delivery of parenteral nutrition is required. Macronutrient (protein, carbohydrate, and fat) delivery, together with correct provision of fluid and electrolytes are vital components of nutritional management, and imbalance results in adverse effects in the short to medium term. Micronutrient deficiency or toxicity may also occur, but the clinical sequelae may be less obvious and are generally of more insidious onset.

Monitoring micronutrient homeostasis has certain difficulties. For certain substances such as iron and folate, there are simple blood tests that indicate whether a deficiency state is present. For many other trace elements and vitamins, blood levels may not reflect body stores, and simple tests of overall micronutrient status are not readily available. Whether deficiency states develop depends on the remaining absorptive capacity of the bowel and the

amount of micronutrients delivered parenterally. For some micronutrients, the daily requirements for healthy individuals are unclear,¹ and the relationship between requirements defined from an oral route of administration and those required when given intravenously is largely unknown.

Reports of micronutrient deficiency in HPN programs have primarily been in the form of clinical anecdotes or peripheral blood estimations of micronutrient levels.²⁻⁴ The extent to which clinically relevant micronutrient deficiency occurs in patients receiving HPN has not been reported. Hence we sought to document the incidence and nature of clinical micronutrient deficiency within our HPN program and relate these findings to the delivery of HPN and to serum concentrations of certain micronutrients.

METHODS AND MATERIALS

Patients

In January 1995, 49 patients were actively receiving HPN at St. Mark's Hospital, London. The presence or previous development

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TABLE I.

PATIENT DETAILS	
Primary diagnosis	
Crohn's disease	20
Visceral myopathy/neuropathy	7
FAP/desmoid tumour	5
Postoperative complications	4
Radiation enteritis	4
Vascular insult	4
Other	5
Duration on HPN	
<2 y	13
2-5 y	13
>5 y	23
Mean duration of HPN: 64 mo (range, 1-175 mo)	

FAP, familial adenomatous polyposis coli; HPN, home parenteral nutrition.

of micronutrient deficiency was sought by clinical assessment at a routine 2-mo outpatient visit, in conjunction with review of case records. Peripheral blood was analyzed for certain micronutrient levels, and the results were correlated with clinical parameters and the type of micronutrient supplementation provided in the nutrient admixture. Estimations of serum iron indices and red cell folate were undertaken at least yearly in the absence of anemia. In a randomly selected group of 32 patients, serum levels of the following micronutrients were also assessed: zinc, copper, selenium, manganese, vitamin A, and vitamin E. Samples were taken through a plastic intravenous cannula inserted into a peripheral vein, at least 6 h after cessation of the intravenous nutrient infusion. The first aliquot of blood taken was discarded and a second sample taken for analysis. Serum stored at -70°C was forwarded to the Department of Clinical Chemistry, University of Liverpool, Liverpool, England for analysis.

Delivery of HPN

The nonprotein energy value of the parenteral nutrition ranged from 1344 to 11 090 kJ/d, (mean, 5270 kJ), given six or seven times weekly in 31 patients, three to five times weekly in 17 patients, and fewer than three times weekly in 1 patient. Most patients ate a variety of foods ad libitum, and many patients had previously taken, or were taking, medications aimed at reducing stool volume (loperamide, codeine phosphate, histamine-2 recep-

tor antagonists, or proton pump inhibitors). Parenteral amino acids were supplied as Freamine III 8.5% (Fresenius; UK) with each infusion, and lipid was given once or twice weekly to 35 patients as Intralipid (Pharmacia; UK). Additional intravenous fluid supplements were given depending on intestinal fluid losses. Supplemental vitamins were administered as intravenous multibionta (Merck; UK), 2-3 ampules weekly, intravenous folic acid (15 mg weekly), intramuscular vitamin B₁₂ (1 mg four times per year) and, in the absence of prothrombotic tendencies, intramuscular phytonadione (10 mg four times per year). One ampule of Multibionta contains ascorbic acid (500 mg), dexpantenol (25 mg), nicotinamide (100 mg), pyridoxine hydrochloride (15 mg), riboflavine sodium phosphate (10 mg), thiamine hydrochloride (50 mg), tocopheryl acetate (5 mg), and vitamin A (10 000 units). The following quantities of trace elements were administered with each daily infusion: zinc (120 μmol), copper (20 μmol), manganese (2 μmol), selenium (0.8 μmol), iodine (1 μmol), and fluoride (50 μmol). Micronutrients (vitamins and trace elements) were added to nutrient admixtures up to 2 wk before administration; the admixtures were then stored at 4°C in dedicated freezers at the patients' home before infusion.

RESULTS

Patient Details and Clinical Micronutrient Deficiency States

Seventeen patients were male and 32 female, with a mean age of 46 y (range, 24-66 y). The underlying disease process for which HPN was being delivered, and the duration of HPN therapy at the time of study, is outlined in Table I.

Clinically relevant micronutrient deficiency was found in 16 (33%) patients. Iron deficiency, resulting in a microcytic anemia developed in 14 patients, 0-8 y (mean, 25 mo) after starting HPN; only two of these patients were receiving iron supplements at the time anemia developed (one intravenously and one orally). Iron deficiency was present in 2 of the 14 patients at the start of HPN therapy; one patient with active Crohn's disease was anemic and receiving supplemental iron, and the other patient was not anemic. In 6 patients, additional factors were likely to have contributed to the development of anemia: active Crohn's disease in 3, upper gastrointestinal bleeding in 2, and menorrhagia in 1. After supplemental iron therapy, the anemia resolved in all patients except one patient who had persistent rectal blood loss.

Of the 14 patients with iron deficiency anemia, 2 were found to have coexistent folate deficiency despite intravenous folate supplementation. This developed after 55 and 96 mo of HPN in patients with radiation enteritis and short gut following resection for Crohn's disease, respectively. Red cell folate levels returned to normal after additional supplementation in both patients.

TABLE II.

PATIENT SERUM LEVELS OF MICRONUTRIENTS						
	Zinc ($\mu\text{mol/L}$)	Copper ($\mu\text{mol/L}$)	Selenium ($\mu\text{mol/L}$)	Manganese ($\mu\text{mol/L}$)	Vitamin A ($\mu\text{mol/L}$)	Vitamin E ($\mu\text{mol/L}$)
Normal laboratory reference range	12.7-20.2	12.8-24.7	0.7-1.6	5-15	1.1-2.8	12-47
No. of patients/ serum levels						
Normal	14	20	27	1	19	15
Low	7	11	5	0	1	17
High	11	1	0	31	12	0
Range	7.8-24.4	8.0-49.9	0.2-1.5	10-43	1.0-5.4	<0.5-38

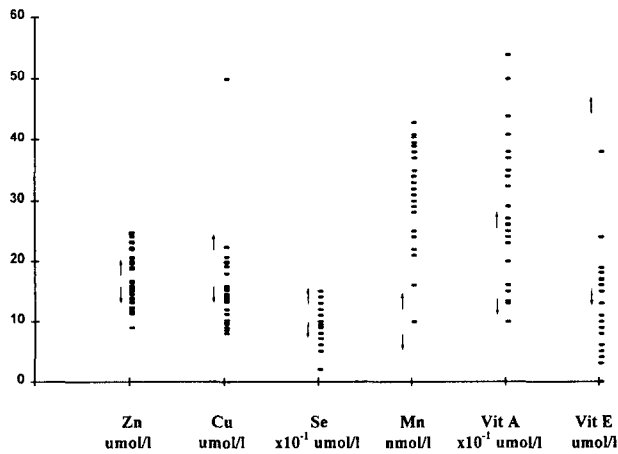


FIG. 1. Serum levels of micronutrients. Normal laboratory reference ranges are indicated by arrows for each micronutrient.

Three patients were believed to be deficient in biotin, manifested by dry eyes, angular cheilitis, and hair loss, although this was not proven by measuring levels of biotin. In all three patients, symptoms resolved after intravenous treatment with biotin. HPN had been given for 4.5, 5, and 9 y to these patients at the time assumed biotin deficiency was diagnosed.

Vitamin A deficiency, manifested by visual disturbance developed in one patient with radiation enteritis, in whom vitamin A had been withheld for 30 mo because of a possible but unconfirmed adverse reaction to previous vitamin A therapy. Symptoms resolved promptly after replacement therapy using an alternative vitamin A preparation.

Micronutrient Assays

Thirty-two randomly selected patients had blood samples taken for serum assays of zinc, copper, selenium, manganese, vitamin A, and vitamin E. All patients had at least one micronutrient level outside the normal laboratory reference range. The laboratory reference ranges for serum levels of these micronutrients and the number of patients with normal, low or high levels are given in Table II. These data are illustrated in Fig. 1. All but one patient had elevated serum levels of manganese. Even when this is taken into account, only two patients had normal serum levels of all other micronutrients. Patients receiving HPN more infrequently (three to five times per week) were no more or less likely to develop either clinical or biochemical micronutrient deficiencies than those receiving HPN daily. When these serum assays were reviewed in conjunction with clinical assessment of patients, it was not possible to identify individuals in whom there was clinical evidence of micronutrient toxicity or deficiency.

DISCUSSION

This study suggests that, although micronutrient abnormality in HPN patients is extremely common, serious sequelae are unusual, and deficiency states are often predictable. In our program, iron deficiency anemia was the most common clinically relevant deficiency state. Anemia occurred in 14 (29%) patients, although in 6 there was concomitant blood loss, which precipitated the development of anemia. We have not routinely given patients iron supplementation for logistic reasons—iron is not compatible with the nutrient admixture given to our patients, as it often causes gastrointestinal upset when given orally, is uncomfortable and discolored when given intramuscularly, and there is a risk of serious adverse reactions when given intravenously as an inde-

pendent infusion. Hence our policy has been to give iron supplementation to HPN patients only when anemia develops in the presence of iron deficiency, and this approach appears to be justified by the outcomes described. When anemia occurs in HPN patients, it is important to consider deficiency of other micronutrients; concomitant folate deficiency was found in two of our patients in this way. Clinical evidence of vitamin A and biotin deficiency occurred in another four patients who were not receiving supplementation of these micronutrients. Although vitamin A is routinely given to patients within our HPN program, biotin is not, due to incompatibility with the preprepared nutrient admixtures.

It should be remembered that the majority of HPN patients will be provided a certain amount of their nutrient requirements orally. This may explain why serious micronutrient deficiencies are uncommon. Furthermore, the micronutrient serum reference ranges provided are only guides, based on healthy individuals. Levels outside this "normal" range may not necessarily reflect functional deficiency or toxic states. Although there are recommended daily oral intakes of most micronutrients, for certain substances such as pantothenic acid and biotin, there is insufficient information to allow for clear-cut recommendations,¹ and there are even greater difficulties extrapolating oral into intravenous requirements. Table III details the American Food and Nutrition Board's recommended daily dietary micronutrient requirements and compares these oral

TABLE III.

MICRONUTRIENT REQUIREMENTS: ORAL DAILY REQUIREMENTS COMPARED WITH PARENTERALLY ADMINISTERED QUANTITIES IN THE ST. MARK'S HOSPITAL HPN PROGRAM*

	Recommended per oral daily dietary requirements	Amount delivered to HPN patients intravenously
Vitamins		
B ₁	1-1.5 mg	15 mg
B ₂	1.2-1.6 mg	3 mg
Nicotinic acid	15-20 mg	30 mg
B ₆	1.6-2.0 mg	4.5 mg
Pantothenic acid	? 4-7 mg†	7 mg
Biotin	? 30-100 µg†	Nil
B ₁₂	2 µg	1 mg IM 4 times per year
C	60 mg	140 mg
Folic acid	200 µg	15 mg once weekly
A	1000 µg	1000 µg
E	8-10 mg	1.5 mg
K	75 µg	10 mg IM 4 times per year
Trace elements		
Iron	10-15 mg	Nil
Zinc	12-15 mg	120 µmol/feeding (8 mg)
Copper	1.5-3.0 mg	20 µmol/feeding (0.13 mg)
Manganese	2-5 mg	5 µmol/feeding (0.28 mg)
Molybdenum	75-250 µg	2 µmol/feeding (190 µg)
Selenium	55-70 µg	0.8 µmol/feeding (63 µg)
Iodine	150 µg	1 µmol/feeding (130 µg)
Fluoride	1.5-4.0 mg	50 µmol/feeding (1 mg)
Chromium	50-200 µg	Nil

HPN, home parenteral nutrition; IM, intramuscular.

* Oral requirements are from the American Food and Nutrition Board.¹

† Precise dietary requirements are uncertain.

recommendations with intravenous doses given in our HPN program.

Our findings of wide variations in serum levels of zinc, copper, selenium, manganese, vitamin A, and vitamin E in the absence of clinical deficiency or toxicity are similar to reports from other HPN centers.²⁻⁴ With the exception of vitamin A, toxicity states of these micronutrients do not, or rarely occur in clinical practice. Manganese toxicity has been reported to result in hepatic and neurotoxicity in pediatric HPN patients,⁵ but we have not found this in our adult population in whom elevated serum manganese levels in this study and elevated red cell manganese in a previous report⁶ were found to be a common occurrence. Conversely, deficiency of zinc, selenium, vitamin A, and vitamin E^{1,7-9} all have clinical sequelae that may not develop for many years, because of ongoing oral intake of food or the time taken to deplete tissue stores of these substances. Furthermore, there might be certain subclinical sequelae in HPN patients from mild disturbances in micronutrient homeostasis, including disturbances in immunologic function that are unquantifiable.¹⁰ Much more work is required to clearly define micronutrient requirements for HPN patients, particularly as they live longer with improved clinical management. In the meantime, clinical judgement will largely dictate micronutrient delivery to these patients.

Our study has a number of limitations, in that it sought to retrospectively document clinical evidence of micronutrient deficiency and has only examined serum levels of certain substances. Blood samples were taken at least 6 h after cessation of the intravenous nutrient admixture, but it is unknown whether longer time is required to allow for a steady-state blood level to devel-

op—this might explain a number of elevated serum levels of manganese, vitamin A, and zinc in our patients. A number of other important micronutrients such as iodine, fluoride, chromium, molybdenum, and certain vitamins were not assayed. Furthermore, functional assessments of some of these substances is perhaps more relevant, such as thyroid function and dental status as markers of iodine and fluoride homeostasis, respectively. Nonetheless, this study serves to illustrate the difficulties experienced in clinical practice when managing these patients. The delivery of parenteral nutrition remains an imprecise art—longevity of patients is related principally to optimal management of the underlying gastrointestinal disease, careful attention to fluid and calorie homeostasis, and prevention of sepsis.¹¹ Delivery of micronutrients remains an important, but still relatively small component of the overall management of these complex patients.

Summary

Although clinical micronutrient deficiency and abnormalities of serum micronutrient levels are common in patients receiving home parenteral nutrition, serious sequelae are unusual. When a deficiency state arises, additional micronutrient supplementation readily corrects this defect in most instances.

ACKNOWLEDGMENT

Acknowledgment and research support: Supported by the FA Hadley Overseas Travelling Scholarship of the University of Western Australia (G.M.F.). We thank Professor A. Shenkin, Department of Clinical Chemistry, Royal Liverpool Hospital, for performing the micronutrient assays.

REFERENCES

1. Food and Nutrition Board. Recommended Dietary Allowances. Washington: National Academy Press, 1989
2. Shils ME, Baker H, Frank U. Blood levels of long-term adult home total parenteral nutrition patients: the efficacy of the AMA-FDA parenteral multivitamin preparation. *JPEN* 1985;9:179
3. Labadarios D, O'Keefe SJD, Dicker J, et al. Plasma vitamin levels in patients on prolonged total parenteral nutrition. *JPEN* 1985;12:205
4. Burnes JU, O'Keefe SJD, Fleming CR, Devine RM, Berkner S, Herrick L. Home parenteral nutrition—a 3 year analysis of clinical and laboratory monitoring. *JPEN* 1992;16:327
5. Fell JME, Reynolds AP, Meadows N, et al. Manganese toxicity in children receiving long-term parenteral nutrition. *Lancet* 1996;347:1218
6. Forbes A, Jawhari A. Manganese toxicity and parenteral nutrition. *Lancet* 1996;347:1774
7. Kawakubo K, Iida M, Matsumoto T, et al. Progressive encephalopathy in a Crohn's disease patient on long-term total parenteral nutrition: possible relationship to selenium deficiency. *Postgrad Med J* 1994;70:215
8. Watson NJ, Hutchinson CH, Atta HR. Vitamin A deficiency and xerophthalmia in the United Kingdom. *Br Med J* 1995;310:1050
9. Traber MG, Schiano TD, Steephen AC, Kayden HJ, Shike M. Efficacy of water-soluble vitamin E in the treatment of vitamin E malabsorption in short-bowel syndrome. *Am J Clin Nutr* 1994;59:1270
10. Shenkin A. Adult micronutrient requirements. In: Payne-James J, Grimble G, Silk D, eds. *Artificial nutrition support in clinical practice*. London: Edward Arnold, 1995:151
11. Messing B, Lemann M, Landais P, et al. Prognosis of patients with non-malignant chronic intestinal failure receiving long-term home parenteral nutrition. *Gastroenterology* 1995;108:1005

(For an additional perspective see Editorial Comment on page 986.)