Original Contribution Kitasato Med J 2012; 42: 148-155

Adequacy of serum concentrations of vitamin and trace element preparations in treating patients with inflammatory bowel disease receiving long-term, home parenteral nutrition

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Objectives: Home parenteral nutrition (HPN) is occasionally used for inflammatory bowel disease (IBD) after extensive small-bowel resection. However, vitamin or trace element deficiencies may occur in patients with enterostomy and intestinal inflammation. To determine whether vitamin or trace element content of supplemental total parenteral nutrition (TPN) preparations was adequate, we evaluated serum of IBD patients receiving long-term HPN.
Methods: Four IBD patients (3 Crohn's disease and 1 intestinal Behçet's disease) on HPN, who had extensive small-bowel resections, were included in the present study. Three patients had ileostomies. Serum levels of vitamins B_1, B_6, C, K, folic acid, iron, zinc, copper, and manganese were measured at baseline, and at 2, 4, and 6 months and compared to reference ranges.
Results: Throughout follow-up, vitamins B1, B6, and folic acid concentrations were within or above reference ranges. In 3 patients, vitamin C concentrations were in the low range; one 6-month value was below range. Vitamin K concentrations were well above range in 3 patients; levels in the fourth patient were also above range. Zinc and copper concentrations were mostly within range, but iron was low in 1 patient and manganese in another.
Conclusions: Vitamin C should be increased and vitamin K decreased in multivitamin preparations for TPN.

Key words: home parenteral nutrition, inflammatory bowel disease, short bowel syndrome, vitamin, trace element

Introduction

Recently, total parenteral nutrition (TPN) and enteral nutrition have been widely used for patients with inflammatory bowel disease (IBD), such as Crohn's disease, and for malabsorption diseases, such as short bowel syndrome. Home parenteral nutrition (HPN) provides long-term nutritional support for patients whose intestinal absorption is difficult or inadequate, and it is effective for shortening hospital stays, improving quality of life, and reducing long-term morbidity and mortality.[1-3] However, as more patients have received long-term HPN, instances of trace-element deficiencies have been reported, [4-11] which has caused an increased recognition of the nutritional importance of these elements. Patients with Crohn's disease receiving HPN have been reported to be deficient in antioxidative vitamins and trace elements and to have increased oxidative stress, even during disease remission.[12-16] Oxidative stress/damage and the inflammatory/immune response may be increased further by psychosocial stress, which may eventually lead to recurrence or aggravation of Crohn's disease. Therefore, patients with IBD who receive long-term HPN should be monitored for potential vitamin or trace element deficiencies. However, few studies have been conducted of serum vitamin or trace element concentrations in IBD patients receiving long-term HPN. Therefore, we measured the time course of serum concentrations of vitamins and trace elements in IBD patients receiving long-term HPN and evaluated whether or not there were any deficiencies.

Received 24 February 2012, accepted 28 March 2012
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Table 1. Clinical characteristics of 4 patients with inflammatory bowel disease receiving long-term home parenteral nutrition

Patient No.	Sex	Age, y	Height, cm	Weight, kg	Disease	Length of residual Intestine, cm	Complications	Duration of HPN, y
1	Male	43	175	53	CD	200	Fistula, ileostomy	11
2	Male	40	163	50	BD	150	Fistula, abscess, ileostomy	3
3	Male	46	162	53	CD	Unknown	Fistula	3
4	Male	55	160	43	CD	140	Chronic renal failure, ileostomy	7

CD, Crohn's disease; BD, intestinal Behçet's disease; HPN, home parenteral nutrition

Table 2. Patients' nutritional intake per day

Patient No.	Home parenteral preparation			Dietary intake	Enteral nutrition (ml)
	Transfusion mixture (Kcal)	Multivitamins supplements (ml)	Trace elements (ml)		
1	Neoparen (1,640)	No	Mineralin (2)	Yes	Racol (400)
2	Neoparen (820) PN-Twin (1,160)	Vitaject kit (5)	Mineralin (2)	No	No
3	Neoparen (820)	Vitaject kit (5)	Mineralin (2)	Yes	Racol (200)
4	Hicaliq (700) Proteamin (182)	Vitaject kit (5)	Mineralin (2)	Yes	No

Neoparen®, Otsuka Pharmaceutical, Naruto, Tokushima
Racol®, EN Otsuka Pharmaceutical, Hanamaki, Iwate
Hicaliq®, Proteamin®, and Vitaject Kit®, Terumo, Tokyo
PN-Twin®, Ajinomoto Pharmaceutical, Tokyo
Mineralin®, Nihon Pharmaceutical, Tokyo

Table 3. Intravenous vitamin and trace element dosage per day

Patient No.	Vitamin					Trace element			
	Vitamin B_1 (mg)	Vitamin B_6 (mg)	Vitamin C (mg)	Folic acid (μg)	Vitamin K (μg)	Iron (mg)	Zinc (mg)	Copper (mg)	Manganese (mg)
1	3.10	4.00	100	400	2,000	1.95	6.53	0.32	0.055
2	3.93	5.27	150	600	3,000	1.95	6.53	0.32	0.055
3	3.93	5.27	150	600	3,000	1.95	5.23	0.32	0.055
4	2.38	3.27	100	400	2,000	1.95	5.23	0.32	0.055

Materials and Methods

Patients

We studied 4 men with inflammatory bowel disease: 3 with Crohn's disease and 1 with intestinal Behçet's disease, who were receiving outpatient care at the Kitasato University East Hospital between November 2008 and October 2009 (Table 1). All had undergone small bowel resection, and their remaining intestinal length ranged from 140 to 200 cm. Two of the patients had an internal fistula and ileostomy, 1 had a fistula, and 1 had an ileostomy. The duration of HPN treatment ranged from 3 to 11 years.

Nutritional support

Table 2 shows the detailed nutritional intake of the patients. The maintenance calories for HPN were adjusted between 820 to 1,980 kcal/day. A syringe of Vitaject Kit® (Terumo, Tokyo), a multivitamin preparation was given to 3 of the 4 patients every day, and an ampoule of Mineralin® (Nihon Pharmaceutical, Tokyo), a trace element preparation for TPN, was given to all the patients every day. Patient No. 1's diet was supplemented with oral food intake, enteral nutrition, and vitamins (B_1, B_2, and B_6). Patient No. 2 was supported solely by HPN. Patient No. 3's diet was supplemented with oral food intake and by enteral nutrition. Patient No. 4's diet was also supplemented with oral food intake and with zinc supplements.

The dosages of intravenous vitamins and trace elements the patients received are shown in Table 3. All of the TPN solutions contained zinc, and Neoparen® (Otsuka Pharmaceutical, Tokushima) as well as multivitamins. The HPN treatment was not altered for at least 1 year before the study was begun.

Study design

The study was approved by the Institutional Ethics Committee of Kitasato University East Hospital. Written informed consent was obtained from all patients.

Blood samples were taken on the first day of the study and at 2, 4, and 6 months' follow-up appointments. The primary outcomes were changes in the serum concentrations of the vitamins (vitamins B_1, B_6, C, K, and folic acid) and trace elements (iron, zinc, copper, and manganese). Secondary outcomes were changes in 3 nutritional indices: serum total protein, serum albumin, and serum total cholesterol. Tests were performed to evaluate safety, routine hematology, and blood chemistry.

Serum concentrations were determined with high-performance liquid chromatography (Wakosil-II U5C18HG, Wako Pure Chemical Industries, Osaka) for vitamins B_1 and B_6; with high performance liquid chromatography (Inertsil® ODS-3, GL Sciences, Tokyo) for vitamin C; with high-performance liquid chromatography (LQODS-UH, FLOM, Tokyo) for vitamin K; with chemiluminescent enzyme immunoassay (UniCel Dex 800, Beckman Coulter, CA, USA) for folic acid; with the Nitroso-PSAP method (BioMajesty JCA-BM8060, JEOL, Tokyo) for iron; with atomic absorption spectrometry (Z6100 Series Polarized Zeeman atomic absorption spectrophotometer, Hitachi, Tokyo) for zinc; with atomic absorption spectrometry (Spectr AA-300, Varian, TX, USA) for manganese; and with the colorimetric method (BioMajesty JCA-BM8000 series, JEOL) for copper.

Results

Changes in vitamin concentrations (Table 4)

The serum vitamin B_1 concentration was greater than the reference range in all patients. The serum vitamin B_6 concentration was much greater than the reference range in Patient No. 1, but was within the range in the other 3 patients. The serum vitamin C concentration was below the reference range at month 6 in Patient No. 1. Patient No. 2 had a value near the lower limit of the range at month 4. Patient No. 3's values remained at the lower limit of the reference range. Patient No. 4 had values within the range throughout the study period. Serum folic acid concentrations were within the reference range in all the patients. Serum vitamin K concentrations were much greater than the reference range in Patients Nos. 1, 2, and 4; Patient No. 3's values were lower than the others but still high. No patients showed signs or symptoms of vitamin excess or deficiency.

Changes in trace element concentrations (Table 4)

Serum iron concentrations were within the reference range in Patients Nos. 2 and 4. Patient No. 1's values were greater than the range at 2 and 4 months, and Patient No. 3's values were below the range on the first day of the study and remained low throughout the study period. Serum zinc concentrations were within or near the reference range in Patients Nos. 1, 2, and 3 but were greater than the range on the first day in Patient No. 4 and remained high. Serum copper concentrations were within or above the reference range in Patients Nos. 1 and 2, above the range throughout the study period in Patient No. 3, and near the lower limit of the range throughout the study in Patient No. 4. Serum manganese concentrations were within or near the reference range in Patients Nos. 2 and

Table 4. Changes of serum vitamins and trace elements throughout the study period

	Reference range	Patient No.	0 months	2 months	4 months	6 months
Vitamins						
B_1	20-50	1	99	76	81	92
(ng/ml)		2	69	79	80	87
		3	51	59	53	57
		4	58	64	58	57
B_6	6.0-40.0	1	551.2	578.4	544.5	524.4
(ng/ml)		2	25.1	37.3	30.7	35.7
		3	13.9	10.9	13.2	10.8
		4	33.3	29.8	36.1	38.5
C	5.5-16.8	1	8.0	6.6	8.2	4.2
(ng/ml)		2	7.4	7.9	5.9	6.8
		3	6.1	6.4	6.0	6.8
		4	9.3	8.5	10.8	9.7
Folic acid	<3.1	1	10.3	11.1	13.2	8.1
(ng/ml)		2	14.8	18.1	11.5	18.4
		3	16.8	15.0	17.5	16.4
		4	17.6	15.6	14.3	16.6
K	0.15-1.25	1	15.12	13.12	15.75	14.21
(ng/ml)		2	6.29	15.27	10.2	16.28
		3	2.2	2.23	2.16	2.23
		4	14.97	19.56	11.17	29.58
Trace elements						
Fe	54-200	1	148	206	239	73
(μg/dl)		2	116	99	97	101
		3	44	32	37	30
		4	181	182	184	177
Zn	65-110	1	75	71	70	61
(μg/dl)		2	89	85	82	92
		3	92	75	97	91
		4	123	112	128	111
Cu	68-128	1	94	112	105	167
(μg/dl)		2	134	107	135	103
		3	129	135	175	156
		4	77	73	71	70
Mn	0.8-2.5	1	0.8	0.8	0.8	0.9
(μg/dl)		2	1.1	1.3	1.2	1.4
		3	2.4	2.6	2.4	2.4
		4	0.6	0.5	0.6	0.6

3, at the lower limit of the range in Patient No. 1, and slightly below the range throughout the study in Patient No. 4. No patients showed signs or symptoms of an excess or deficiency of trace elements during the study period.

Changes in nutritional indices (Table 5)

Serum total protein levels remained within the reference range in all patients. Serum albumin levels were below the reference range in Patients Nos. 3 and 4 (especially in Patient No. 3), below at 2 and 4 months in Patient No. 2, and below at 6 months in Patient No. 1. Total cholesterol levels remained below the reference range throughout the study in all the patients.

Safety evaluation (Table 5)

Changes in the major hematological or blood chemistry values are also shown in Table 5. No values deviated greatly from the reference range during the study. However, Patients Nos. 1, 2, and 3 had elevated C-reactive protein (CRP) levels, which were probably attributable to catheter-related infection or worsening of their underlying disease. In Patient No. 4, the red blood cell

Table 5. Changes of serum characteristics throughout the study period

	Reference range	Patient No.	0 months	2 months	4 months	6 months
Nutritional indices						
Total protein (g/dl)	6.7-8.3	1	7.6	7.8	8.1	7.8
		2	7.4	6.6	7.0	7.4
		3	7.0	7.3	7.7	7.7
		4	7.4	7.1	7.5	7.3
Albumin (g/dl)	4.0-5.0	1	4.4	4.5	4.6	3.4
		2	4.2	3.9	3.9	4.4
		3	3.2	3.2	3.3	3.1
		4	3.8	3.5	3.8	3.6
Total cholesterol (mg/dl)	150-219	1	114	115	119	97
		2	86	77	87	77
		3	87	92	89	77
		4	98	93	100	94
Complete blood count and CRP						
Red blood cell count/10^4	427-570	1	406	430	431	390
		2	484	449	471	503
		3	418	412	413	375
		4	334	314	321	304
Hemoglobin (g/dl)	13.5-17.6	1	15.4	15.7	15.8	13.7
		2	15.2	14.2	14.8	15.6
		3	13.2	13.1	12.7	11.5
		4	11.1	10.4	10.8	9.9
Hematocrit (%)	39.8-51.8	1	43.3	46.2	45.1	41.1
		2	46.9	43.5	45.6	47.4
		3	41.2	39.8	39.7	36.4
		4	34.7	32.3	33.4	32.1
Platelet count/10^4	13.1-36.2	1	28.3	32.2	29.8	14.5
		2	19.3	16.2	16.5	12.9
		3	19.9	19.8	22.0	19.6
		4	9.7	7.9	8.2	7.9
C-reactive protein (mg/dl)	>0.30	1	0.12	0.25	0.22	5.28
		2	0.98	0.19	6.23	1.47
		3	1.53	3.53	3.43	1.63
		4	0.02	0.01	0.01	0.01

count, serum hemoglobin level, serum hematocrit level, and platelet count remained below the reference range throughout the study.

Discussion

In the present study, we measured the time course of serum concentrations of vitamins and trace elements in patients with IBD receiving long-term HPN and evaluated if there was an excess or deficiency of vitamins or trace elements. Serum vitamin C concentrations in 3 of 4 patients decreased to at or below the lower limit of the reference range. Shils et al.[17] gave patients receiving HPN a multivitamin preparation once a day for 5 to 8 months and regularly measured serum vitamin concentrations. As in this study, many of their patients had lower vitamin C levels than the reference range. Matsubara et al.[18] reported a decrease in vitamin C content in solution over time to 86.5% of the Day 1 value, if an ampoule of a trace element preparation (2 ml) containing iron, zinc, copper, manganese, and iodine was mixed with a bag of TPN solution (1,000 ml) with multivitamins. In the present study, trace element preparations were also mixed daily with TPN solutions, so the actual daily dose of vitamin C given intravenously might have been below the range of 100 to 150 mg. The lower vitamin C concentrations in the 3 patients were associated with increased CRP levels, indicating that more vitamin C was needed to alleviate the increased oxidative stress induced by inflammation due to infection or worsening of the patients' underlying disease. Others[19,20] have reported that vitamin C deficiency and decreased activity of dehydroascorbic acid reductase in patients with IBD delayed the recovery of inflammatory mucous membranes and that vitamin C deficiency might be involved in fistula formation in Crohn's disease. Therefore, in IBD patients who require HPN, maintaining vitamin C levels within the reference range is crucial, and our study results suggest that the vitamin C content in multivitamin preparations for TPN available in Japan (100 mg) is insufficient.

Serum vitamin K concentrations in 3 of 4 patients remained much higher than the reference range. In Japan, the vitamin K content in multivitamin preparations for TPN is 2,000 μg, and in the present study, 2,000 to 3,000 μg of vitamin K was given daily intravenously. In the United States, however, multivitamin preparations contain just 150 μg of vitamin K. Therefore, we consider that the vitamin K content of multivitamin preparations in Japan is exceedingly high. Recently, there have been occasional reports[21,22] of drug interactions between warfarin and multivitamin preparations used in TPN. Warfarin, an anticoagulant, prevents venous thrombosis by irreversibly inhibiting vitamin K-dependent epoxide reductase and vitamin K quinine reductase. Therefore, in patients with high levels of vitamin K, warfarin's effect is lessened. Pedersen et al.[23] reported that an approximately 1,000-μg increase in vitamin K intake, even for a day, resulted in greatly enhanced blood coagulation. Prolonged intake of vitamin K doubled the effect, and affected blood coagulation for several days even after normal food intake was resumed. In patients with IBD, blood is more coagulable, thus increasing the risk of venous thrombosis.[24] To avoid this risk, less vitamin K should be used in multivitamin preparations for TPN given to IBD patients, especially those on long-term HPN.

Administering a trace element preparation with TPN once daily should prevent deficiencies, at least for the formulated trace elements. Trace element deficiencies are, however, more likely to occur in patients with Crohn's disease, which affects the small intestines. Deficiencies are even more likely to occur in patients with short bowel syndrome who require long-term HPN nutritional support because, in this syndrome, nutrients are lost through malabsorption or inflammation of the intestines. In the present study, serum iron concentrations in 3 of 4 patients remained within or above the reference range. However, the concentration in Patient No. 3 was below the reference range throughout the study, and he was anemic. We attributed this mild iron deficiency to iron malabsorption and chronic bleeding, from the affected site, as a result of Crohn's disease. In a study in the United Kingdom,[13] researchers found that 16 of 49 patients with intestinal failure, who had received long-term HPN, had symptoms of trace element deficiencies; 14 patients (29%) had iron-deficiency anemia, but most recovered with iron supplementation.

Patients with IBD who require long-term HPN often have low serum zinc concentrations, and these patients may need more supplemental zinc than the dose recommended for patients with other diseases. Serum zinc concentrations in Patients Nos. 2, 3, and 4 remained within or above the reference range. However, the concentration in Patient No. 1 remained mostly at the lower limit of the reference range. Zinc malabsorption in short bowel syndrome is affected by the length of the remaining small intestine, and patients with high stoma output tend to lose large amounts of zinc.[25] Patient No. 1 had an ileostomy with an intestinal length of 200 cm and had a low serum zinc concentration, probably as a result of substantial drainage from the ileostomy.

In 1972, Karpel et al.[6] were the first to report copper deficiency in a patient receiving TPN. Since then, many

other instances have been reported.[7-9] Crohn's disease is not known to cause lower serum copper concentrations,[26,27] but more than half of patients with Crohn's disease may have low copper concentrations.[12] In the present study, Patient No. 4 consistently had a serum copper concentration at the lower limit of the reference range. Copper deficiency can cause anemia and leucopenia; and red blood cell count, serum hemoglobin level, serum hematocrit level, and platelet count, in Patient No. 4, were below the reference ranges. On the other hand, the serum copper concentration in Patient No. 3 was above the reference range. Serum ceruloplasmin and copper concentrations increase in patients with infection, inflammation, or cancer, or who are pregnant. Levels of C-reactive protein in Patient No. 3 also increased throughout the study, probably because of the increase in serum copper concentration. The copper concentration in Patient No. 1 was greater at month 6, as was his C-reactive protein level, indicating inflammation, which probably explains the increased serum copper concentration. In the present study, changes in the serum manganese concentration were also evaluated and remained constant in all patients throughout the study.

In patients with IBD who require long-term HPN, such as in Crohn's disease, vitamins and trace elements are not absorbed well, and the amount of vitamins and trace elements lost is often greater and may be even higher in patients with short bowel syndrome or enterostomy. The amount of supplemental vitamins or trace elements needed for such patients varies by the disease and by the condition of the intestines. Therefore, serum concentrations should be measured periodically to monitor for excesses or deficiencies.

These results from measuring the time course of serum concentrations of vitamins and trace elements in IBD patients receiving long-term HPN revealed that the composition of multivitamin preparations for TPN should have increased vitamin C content and decreased vitamin K content.

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