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Zinc and copper balance studies in infants receiving total parenteral nutrition[1-4]

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ABSTRACT To determine the adequacy of zinc and copper supplementation for infants receiving total parenteral nutrition (TPN), we performed 24-h balance studies in infants with diarrhea and infants who had recently undergone surgery. Measurements were made at base line, 1, and 2 wk. Mean serum Zn and Cu levels of the diarrhea group remained normal and were low in the postoperative group but normalized over the study period. Mean 24-h Zn and Cu balances were positive in infants with diarrhea and negative in postoperative infants. The high Zn and Cu content in the gastrointestinal fluid loss associated with surgery may have accounted in part for this finding. Normal serum levels of Zn and Cu did not guarantee positive balance. No significant changes were found in serum albumin, alkaline phosphatase, or ceruloplasmin. The current Zn and Cu recommendations may be appropriate only for hospitalized infants who have no excessive gastrointestinal fluid losses. *Am J Clin Nutr* 1989; 49:879–83.

KEY WORDS Serum zinc, serum copper, total parenteral nutrition, serum albumin, alkaline phosphatase, ceruloplasmin

Introduction

Numerous investigators have attempted to determine the amounts of zinc and copper required by infants who receive total parenteral nutrition (TPN). However, most of these studies have addressed the needs of premature infants (1–4). Researchers who have studied the needs of full-term or older infants have either made serial measurements of Zn and Cu serum levels or performed balance studies only in newborns (4, 5). In a balance study conducted by Zlotkin and Buchanan (4) in newborns, no discrimination was made between infants with medical and surgical illnesses. Surgery and its associated stress are likely to affect trace mineral status. The importance of definitive research on Zn and Cu requirements in children who receive TPN is underscored by the reported clinical manifestations of Zn and Cu deficiencies in infants who receive TPN (6–8).

Although Zn and Cu serum concentrations can provide some insight into Zn and Cu status, the measurements can be affected by many factors such as stress, drugs, and serum proteins (9). Decreases in serum albumin, for example, can decrease serum Zn because of binding. When properly performed, balance studies of Zn and Cu probably provide the best readily available assessment of Zn and Cu nutriture (9). Measurements of alkaline phosphatase and ceruloplasmin provide additional albeit less sensitive measures of Zn and Cu status, respectively.

The objective of our study was to determine serum concentrations and 24-h balances of Zn and Cu in a group of infants who received TPN. By studying infants past the newborn period, using the balance technique, we provide a greater insight into the Zn and Cu status of this group of patients than has been achieved in previous studies. The amounts of Zn and Cu provided to the infants were within the ranges recommended by the Nutrition Advisory Group of the American Medical Association in 1979 (Zn, 1.5 $\mu mol \cdot kg^{-1} \cdot d^{-1}$; Cu, 0.3 $\mu mol \cdot kg^{-1} \cdot d^{-1}$) (10).

Materials and methods

Patient population

Thirteen infants (six with chronic diarrhea, seven recovering from surgery) were studied (**Tables 1 and 2**). We attempted to

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TABLE 1
Intake, serum zinc and copper, and 24-h balance values in infants with diarrhea

	Intake		Serum values*						24-h balances					
			Zinc			Copper			Zinc†			Copper		
Age	Energy	Protein	Base line	1 wk	2 wk	Base line	1 wk	2 wk	Base line	1 wk	2 wk	Base line	1 wk	2 wk
mo	*kcal·kg⁻¹·d⁻¹*	*g·kg⁻¹·d⁻¹*		*μmol/L*			*μmol/L*			*μmol·kg⁻¹·d⁻¹*			*μmol·kg⁻¹·d⁻¹*	
6	114	2.9	4.7	8.6	10.6	12.3	20.0	23.6	1.4	1.2	1.3	0.2	0.1	0.1
2	88	4.4	11.3	8.1	10.7	13.9	14.8	13.9	0.1	0.9	ND‡	0.0	0.1	ND
2	140	3.3	9.2	9.6	8.9	16.5	14.0	13.5	0.6	1.0	0.9	0.1	0.1	0.1
1.5	113	4.3	9.3	8.0	13.9	10.7	14.5	13.5	0.8	1.0	1.2	0.1	0.1	0.1
10	130	4.0	8.9	9.2	8.4	13.9	19.0	14.0	1.0	0.5	1.6	0.2	0.2	0.2
2	140	3.6	9.8	11.9	9.2	17.9	11.8	13.5	0.8	1.0	1.2	0.1	0.1	0.1
$\bar{x}$ ± SD 3.9 ± 3.4	122 ± 20	3.8 ± 0.6	8.9 ± 2.1	9.3 ± 1.5	10.3 ± 2.0	14.2 ± 2.7	15.7 ± 3.2	15.3 ± 4.1	0.8 ± 0.4	0.9 ± 0.2	1.3 ± 0.2	0.1 ± 0.1	0.1 ± 0.0	0.1 ± 0.0

* Normal serum zinc, 8–24.9 μmol/L; normal serum copper, 10.2–22.8 μmol/L.
† $p < 0.05$.
‡ Not done.

enroll all term infants who were expected to require more than 1 wk of TPN and who were receiving no enteral intake. Severity of illness was not a criterion. The investigation was approved by the Institutional Review Boards for Human Research at Baylor College of Medicine and the Harris County Hospital District and by the Clinical Investigations and Publications Committee at Texas Children's Hospital. Informed consent was obtained from the parents.

Design

Infants were enrolled during the first 24 h of TPN administration. Zn (1.5 $\mu mol \cdot kg^{-1} \cdot d^{-1}$) and Cu (0.16 $\mu mol \cdot kg^{-1} \cdot d^{-1}$) were added to the TPN solution (Multitrace Pediatric®, Rohrer Group, Inc, Fort Washington, PA). Base-line blood samples were collected for the determination of serum Zn and Cu. A base-line balance study was performed over 24-h and serum Zn and Cu and 24-h balances were performed weekly thereafter. Serum albumin, alkaline phosphatase, and ceruloplasmin were measured at base line and at the end of the study.

Methods

Samples of the TPN solution were obtained for measurement of Zn and Cu before the trace elements were added. The solutions themselves contained insignificant amounts of Zn and Cu. All materials used for collections were determined to be free of trace metal contamination before use. During the balance studies, all excreta (ie, urine, stool, nasogastric and ostomy drainage, excluding skin losses) were collected. The total volume was measured and an aliquot was taken. Blood samples were spun immediately and serum and excreta were stored at −20 °C until analyzed. The volume of TPN infused during the 24-h collection period was noted and the amounts of Zn and Cu infused during this period were calculated. Balance was defined as total intake minus total output for the 24-h period (excluding skin losses).

Analyses

Zn and Cu were analyzed by atomic absorption spectrophotometry (Perkin Elmer Corp, Norwalk, CT). Samples of excreta

TABLE 2
Intake, serum zinc and copper, and 24-h balance values in postsurgical infants

	Intake		Serum values*						24-h balances					
			Zinc			Copper†			Zinc			Copper		
Age	Energy	Protein	Base line	1 wk	2 wk	Base line	1 wk	2 wk	Base line	1 wk	2 wk	Base line	1 wk	2 wk
mo	*kcal·kg⁻¹·d⁻¹*	*g·kg⁻¹·d⁻¹*		*μmol/L*			*μmol/L*			*μmol·kg⁻¹·d⁻¹*			*μmol·kg⁻¹·d⁻¹*	
2	93	3.5	5.4‡	15.1	ND§	7.1	22.0	ND	1.0	−0.8	ND	−0.3	0.1	ND
0.5	92	2.8	9.2	6.3	ND	7.7	16.1	ND	−0.7	1.4	ND	0.0	0.2	ND
0.25	115	2.2	10.0	6.9	8.4	3.6	5.7	4.6	−8.2	−1.3	0.0	−1.7	−0.5	0.1
0.25	103	2.4	7.0	11.0	ND	8.5	9.0	ND	−1.1	0.7	ND	−0.1	0.1	ND
0.25	122	2.6	15.6	14.4	16.2	16.5	15.4	15.3	−3.0	−0.3	−0.1	−0.4	−0.1	0.0
1.50	108	2.2	6.9	11.9	23.0	10.2	6.6	13.7	−3.2	−0.1	−1.3	−0.1	−0.1	−0.1
0.25	90	2.6	8.7	8.9	7.7	13.9	16.1	12.4	1.4	−0.3	0.5	0.1	0.1	0.1
$\bar{x}$ ± SD 0.7 ± 0.7	104 ± 13	2.6 ± 0.5	9.0 ± 3.4	10.7 ± 3.5	13.8 ± 7.2	9.6 ± 4.4	13.1 ± 6.0	11.5 ± 4.7	−1.6 ± 3.3	−0.1 ± 0.9	−0.2 ± 0.8	−0.3 ± 0.7	0.0 ± 0.2	0.0 ± 0.2

* Normal serum zinc, 8–24.9 μmol/L; normal serum copper, 10.2–22.8 μmol/L.
† $p = 0.088$.
‡ Underline indicates time of last sample in which infant had excess gastrointestinal drainage.
§ Not done.

were ashed in a muffle furnace before analysis (Partlow, Hotpack Corp, Philadelphia, PA). Standard curves were established and standards were used to ensure the accuracy of the measurements. Serum albumin was measured by using the bromocresol green dye-binding method, alkaline phosphatase by using a kinetic enzyme assay employing paranitrophenyl phosphate as a substrate, and ceruloplasmin with an immunonephelometric technique (Beckman, Palo Alto, CA). The CV in the methods was ≤ 5%.

Data analyses

A paired *t* test was used to determine the significance of changes in serum Zn and Cu levels and the 24-h balance studies done at base line and 1 wk, and between the initial and final albumin, alkaline phosphatase, and ceruloplasmin determinations. For infants who were studied for 2 wk, regression analysis was used to obtain the slope of the changes in serum Zn and Cu values and balance study values vs time on the individual subjects. The significance of the change in the values for the group was then assessed with a *t* test. Results are expressed as mean ± SD.

Results

All six infants with chronic diarrhea received appropriate calories and protein (Table 1) and gained appropriate amounts of weight (11). One infant had a low serum Zn value when the base-line measurement was made but the value was in the normal range after 1 wk (Table 1). No significant change was seen in the serum Zn values of these infants between base line and 1 wk or during the 2-wk study period. All infants were in positive Zn balance at base line and remained so throughout the study period. There was a significant increase in Zn balance over the 2-wk study period (Table 1: $p < 0.03$).

Serum Cu values were normal throughout the study period and no significant change was observed with time (Table 1). As with Zn balance, Cu balance was positive in all infants and remained so during the study period. No significant change in Cu balance occurred during the study period.

The caloric and protein intake resulted in appropriate growth in all seven infants studied postoperatively. All 13 infants (Tables 1 and 2) received intravenous lipid, which accounted for ~20% of their nonprotein energy intake.

In contrast to the infants with diarrhea, three of the seven postoperative infants had low serum Zn at base line. By 1 wk, however, their values had returned to normal. At 1 wk, two other infants developed low serum Zn values (Table 2). Most of the infants were in negative Zn balance at base line (Table 2). No significant change in mean Zn balance occurred in those in the postoperative group although in five of the infants their Zn balance became less negative or positive by the end of the first week (Table 2).

Most of the postoperative infants had either low or borderline low serum Cu values at base line (Table 2). There was a trend for serum Cu to increase significantly by 1 wk ($p = 0.088$). In two of four infants, serum Cu returned to normal by 1 wk. Of the infants studied at 2 wk, only one had a low serum Cu value. This infant was studied for 3 wk, at which time his serum Cu value was close to normal. As in the case of Zn balance, Cu balance commonly was negative at base line (Table 2). No significant change was found in Cu balance during the study period, primarily because of infant 6 whose Cu balance worsened (Table 2).

Abnormal values for serum Zn and Cu and negative 24-h balances generally occurred during the period in which the infants had excess gastrointestinal drainage (Table 2). Analyses of nasogastric fluids revealed mean Zn and Cu concentrations of 19.9 ± 7.7 and 2.9 ± 2.0 μmol/L, respectively. Ostomy drainage had higher concentrations of both Zn, 394.9 ± 179.5 μmol/L; and Cu, 118.4 ± 53.8 μmol/L.

There was a trend for albumin to increase significantly in infants with diarrhea (**Table 3**; $p = 0.10$). In neither group was there a significant change in alkaline phosphatase or ceruloplasmin (Table 3). No infant in either group manifested clinical signs of Zn or Cu deficiency.

Discussion

The serum Zn and Cu levels designated as normal by our institution are in good agreement with those previously published (5). However, we found striking differences between the results for serum Zn and Cu and 24-h balances obtained in infants with diarrhea compared with those in postoperative infants (Tables 1 and 2).

Postoperative infants, more frequently than infants with diarrhea, had abnormal values for serum Zn and Cu (Tables 1 and 2). Bacterial endotoxin may cause a decrease in serum Zn concentrations, and corticosteroids can do the same to serum Cu values (9). Thus, the greater incidence of low serum Zn and Cu in the postoperative group compared with the infants with diarrhea may reflect factors related to surgery rather than deficiency per se.

All the infants with diarrhea had positive 24-h Zn and Cu balances. In contrast, the base-line Zn and Cu balance studies done in the immediate postsurgical period, when TPN was begun, were negative in most of the postoperative infants (Tables 1 and 2). The postsurgical catabolic period may have increased Zn and Cu excretion and accounted in part for the negative 24-h balances. Nevertheless, the postoperative infants all had excess gastrointestinal drainage. Analysis of this fluid showed it to be rich in both Zn and Cu. Although noted previously, this finding has not been emphasized (6, 12, 13). The gastrointestinal fluid loss is likely to have contributed to the maintenance of the negative balance state of some of the postoperative infants over the 2 wk of study. Infants 3 and 6 who had gastrointestinal fluid losses from base line through the balance study at 2 wk had the most negative Zn and Cu balances (Table 2). Although diarrheal fluid also may be rich in Zn and Cu, stool output de-

TABLE 3
Results of biochemical determinations of infants studied 1 or 2 wk

	Albumin		Alkaline phosphatase		Ceruloplasmin	
	Initial	Final	Initial	Final	Initial	Final
	g/L		μ/L		mg/L	
Infants with diarrhea	3.0	3.5	224	228	200	440
	3.8	3.2	181	60	200	200
	3.8	4.1	349	123	240	220
	2.5	3.5	106	129	170	200
	2.2	2.9	64	75	250	270
	2.7	3.4	89	297	220	280
$\bar{x} \pm$ SD	3.0 ± 0.7*	3.4 ± 0.4*	169 ± 107	152 ± 92	210 ± 30	270 ± 90
Postsurgical infants	3.0	2.5	44	62	180	460
	2.0	2.8	102	233	140	180
	3.9	3.3	40	40	120	250
	3.2	3.1	43	141	240	120
	2.6	2.0	146	85	300	260
	2.2	2.0	73	113	310	230
	2.5	3.5	66	158	140	310
$\bar{x} \pm$ SD	2.8 ± 0.7	2.7 ± 0.6	73 ± 39	119 ± 65	200 ± 80	260 ± 110

* $p < 0.10$.

creased rapidly in the infants with diarrhea when they received TPN.

It is interesting to note that serum concentrations of Zn and Cu returned to normal in some postoperative infants despite their being in negative balance for these trace minerals (Table 2). As previously suggested, therefore, balance studies are more sensitive indicators than serum determinations of Zn and Cu status (9). Serial serum determinations are useful from a practical consideration compared with 24-h urine and stool collections but major changes in Zn and Cu status may be missed.

The results of the Zn and Cu balances found in the study infants who were generally ill, and often had excessive Zn and Cu losses, are difficult to compare with those obtained from normal infants, who by definition have no excessive losses. For example, the amino acids in TPN have been shown to increase zincuria (14). A comparison of infants receiving TPN with normal infants is made all the more difficult because of the paucity of data concerning Zn and Cu balances in normal infants. Cavell and Widdowson (15) have shown that newborn infants are commonly in negative Zn and Cu balance but they studied infants only during the first week of life. In contrast, Scoular (16) demonstrated that preschool children are in positive Zn balance although only a few subjects were studied. A recent study (17) suggests that infants are in positive Zn balance by 36 wk gestation.

The Zn and Cu supplementation level in our study was lower than that used by Dahlstrom et al (5) (Zn 30.6 μmol/L, Cu 15.7 μmol/L). In their study mean serum Zn in the TPN group was significantly higher than in the orally fed control group whereas serum Cu was similar (5). Zlotkin and Buchanan (4) carried out Zn and Cu balance studies in premature, full-term, and full-term, small-for-gestational-age (SGA) infants receiving TPN. Their data suggested that > 2.3 $\mu mol \cdot kg^{-1} \cdot d^{-1}$ of Zn and > 0.25 $\mu mol \cdot kg^{-1} \cdot d^{-1}$ of Cu were needed to achieve positive balances of these minerals (4). A direct comparison with their data is difficult because of the heterogeneity and younger age of their patients (mean age, premature 35 d; full-term 9 d; SGA 13 d) (4). Most importantly, the infants in their study were not separated by medical and surgical diagnoses (4). Thus, excessive gastrointestinal fluid loss was likely in some of their infants, as in some of those in our study, thereby increasing Zn and Cu needs.

No alterations were found in serum albumin, ceruloplasmin, nor the Zn-dependent enzyme, alkaline phosphatase (Table 3) (9). Changes in these serum biochemistries are likely to be found only in severe or prolonged cases of Zn or Cu deficiency.

The results of our study should be applicable to similar infants encountered in clinical practice. Our data suggest that 1.5 $\mu mol \cdot kg^{-1} \cdot d^{-1}$ of Zn and 0.16 $\mu mol \cdot kg^{-1} \cdot d^{-1}$ of Cu may be appropriate for nonsurgical infants who receive TPN for a short term. Additional supplementation may be required by postoperative infants. ■

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References

1. Friel JK, Gibson RS, Peliowski A, Watts J. Serum zinc, copper, and selenium concentrations in preterm infants receiving enteral

nutrition or parenteral nutrition supplemented with zinc and copper. J Pediatr 1984; 104:763–8.
2. Tyrala EE. Zinc and copper balances in preterm infants. Pediatrics 1986;77:513–7.
3. Lockitch G, Godolphin W, Pendray MR, Riddell D, Quigley G. Serum zinc, copper, retinol-binding protein, prealbumin, and ceruloplasmin concentrations in infants receiving intravenous zinc and copper supplementation. J Pediatr 1983;102:304–8.
4. Zlotkin SH, Buchanan BE. Meeting zinc and copper intake requirements in the parenterally fed preterm and full-term infant. J Pediatr 1983;103:441–6.
5. Dahlstrom KA, Ament ME, Medhrin MG, Meurling S. Serum trace elements in children receiving long-term parenteral nutrition. J Pediatr 1986;109:625–30.
6. Weber TR, Sears N, Davies B, Grosfeld JL. Clinical spectrum of zinc deficiency in pediatric patients receiving total parenteral nutrition. J Pediatr Surg 1981;16:236–40.
7. Latimer JS, McClain CJ, Sharp HL. Clinical zinc deficiency during zinc-supplemented parenteral nutrition. J Pediatr 1980;97:434–7.
8. Heller RM, Kirchner SG, O'Neill JA, et al. Skeletal changes of copper deficiency in infants receiving prolonged total parenteral nutrition. J Pediatr 1978;92:947–9.
9. Solomons NW. On the assessment of zinc and copper nutriture in man. Am J Clin Nutr 1979;32:856–71.
10. American Medical Association. Guidelines for essential trace element preparations for parenteral use. JPEN 1979;3:263–7.
11. Shulman RJ, Klish WJ. Total parenteral nutrition in infants. In: Gellis SS, Kagan BM, eds. Current pediatric therapy. New York: WB Saunders Co, 1986:8–11.
12. Wolman SL, Anderson GH, Marliss EB, Jeejeebhoy KN. Zinc in total parenteral nutrition: requirements and metabolic effects. Gastroenterology 1979;76:458–67.
13. Shike M, Roulet M, Kurian R, Whitwell J, Stewart S, Jeejeebhoy KN. Copper metabolism and requirements in total parenteral nutrition. Gastroenterology 1981;81:290–7.
14. Jeejeebhoy KN. Zinc and chromium in parenteral nutrition. Bull NY Acad Med 1984;60:118–24.
15. Cavell PA, Widdowson EM. Intakes and excretions of iron, copper, and zinc in the neonatal period. Arch Dis Child 1964;39:496–501.
16. Scoular FI. A quantitative study, by means of spectrographic analysis, of zinc in nutrition. J Nutr 1939;17:103–13.
17. Higashi A, Ikeda T, Iribe K, Matsuda I. Zinc balance in premature infants given the minimal dietary zinc requirement. J Pediatr 1988;112:262–6.