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Carnitine status of children receiving long-term total parenteral nutrition: A longitudinal prospective study

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Nine children receiving carnitine-free total parenteral nutrition for 7.2 ± 2.6 years since birth were prospectively studied for 3 years. Plasma values of total and free carnitine were 50% lower than those of age-matched healthy control subjects ($p < 0.02$) but did not decrease further during the 3-year period. No significant abnormalities in free fatty acids, triglycerides, or cholesterol were found. The mean levels of alanine and aspartate aminotransferases and of alkaline phosphatase were slightly increased ($p < 0.02$) at the initiation of the study but remained in the same range 3 years later. The low plasma carnitine values appeared to be without clinical consequence after 10 years of carnitine-free total parenteral nutrition. (J PEDIATR 1992;120:759-62)

Carnitine (β-hydroxy-γ-trimethylaminobutyric acid) is required metabolically for the transport of long-chain fatty acids into the matrix of the mitochondria, the site of β-oxidation.[1] Carnitine also functions in the oxidation of very long chain fatty acids in the peroxisomes, in the oxidation of medium-chain fatty acids in the muscle, and in the removal of the acyl group before accumulation to toxic levels. Carnitine is synthesized in the liver and kidney from the essential amino acids lysine and methionine.[2]

We have previously described low plasma carnitine levels in children receiving total parenteral nutrition.[3] The absence of exogenous carnitine may be associated with abnormal oxidation of long-chain fatty acids and progressive hepatic dysfunction. In this study, we assessed the plasma carnitine status in children receiving long-term TPN longitudinally during a 3-year period.

METHODS

Thirteen children totally dependent on parenteral nutrition were investigated prospectively from 1987 to 1990. Four subjects were excluded from analysis because their parenteral nutrition composition was changed significantly after the first year of the study. The remaining nine children

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Table. Parenteral intake and values for total and free carnitine, free fatty acid, cholesterol, triglycerides, ALT, AST, and alkaline phosphatase at the initiation of the study and 3 years later

	Control values	Initiation of study	End of study (after 3 yr)
Caloric intake (kilojoules/kg/day)		285 ± 56	274 ± 62
Fat intake (gm/kg/day)		0.9 ± 0.4	0.8 ± 0.5
Nitrogen intake (mg/kg/day)		250 ± 32	278 ± 58
Total carnitine (mg/dl)	1.27† ± 0.19	0.60 ± 0.17	0.65 ± 0.12
Free carnitine (mg/dl)	0.91† ± 0.20	0.38 ± 0.16	0.60 ± 0.11
Free fatty acids (mmol/L)	0.70 ± 0.40	0.76 ± 0.31	0.73 ± 0.47
Cholesterol (mg/dl)	160* ± 90	129 ± 30	137 ± 46
Triglycerides (mg/dl)	92 ± 63	91 ± 51	98 ± 74
ALT (U/L)	16† ± 15	59 ± 29	54 ± 24
AST (U/L)	21† ± 15	79 ± 40	56 ± 19
Alkaline phosphatase (U/L)	250 ± 80	239 ± 77	222 ± 48

Values are expressed as mean ± SD.
All differences between study subjects at initiation and 3 years later were not significant (*t* test for paired observations).
*p <0.0 control subjects versus study subjects either at study initiation or 3 years later.
†p <0.2 control subjects versus study subjects either at study initiation or 3 years later.

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
TPN	Total parenteral nutrition

were 7.2 ± 2.6 years of age in 1987 and had received TPN since birth for short-bowel syndrome (n = 8) or chronic intestinal pseudo-obstruction (n = 1). In 1990, they had been receiving TPN without carnitine supplementation for 10.2 ± 2.6 years. The children had normal height and weight and normal vitamin status.[4] The daily caloric intake, fat intake from an intravenously administered lipid emulsion (Intralipid 20%; KabiVitrum, Alameda, Calif.), and protein intake from a crystalline L-amino acid injection (Travasol; Baxter Travenol, Deerfield, Ill.) did not significantly differ between initiation of the study and 3 years later (Table). Fat represented 13.2% ± 1.6% of the total caloric support. Parenteral nutrition solutions were infused for 10 to 14 hours through a pediatric or standard Broviac catheter inserted into a central vein. All subjects were estimated to absorb less than 10% of their ingested nutrients, which ranged from 15 to 59 kilojoules per kilogram per day.

Fasting venous blood samples were obtained from the patients at their visit to the TPN clinic 6 hours after completion of the daily TPN infusion. Plasma total and free carnitine were determined after chloroform-methanol extraction by an enzymatic radioisotopic method.[3] Twenty healthy children of the same age range were used for comparison of carnitine values. Values for plasma total and free carnitine, plasma total free fatty acids, serum triglycerides, total cholesterol, total bilirubin, ALT, AST, and alkaline phosphatase were compared at the study initiation and 3 years later. Correlation between carnitine levels and subjects' ages, TPN duration, nutrition solution composition, and values for total free fatty acids, triglycerides, cholesterol, and hepatic aminotransferases were determined at the study initiation and 3 years later. The study was approved by the human subjects protection committee, and informed consent was obtained from the parents of the subjects.

All results were expressed as the mean ± SD. Comparisons between means were done with analysis of variance, analysis of covariance, or the Student *t* test. The association between continuous variables was estimated with the Pearson correlation coefficient or the Spearman rank correlation when the distributions were not normally distributed. Multiple regression analysis was employed.

RESULTS

Mean total and free carnitine values in the patients were 50% of control values. After a 3-year period of TPN, the total carnitine level decreased to 73%, 82%, 84%, and 86%, respectively, of its initial value in four patients, remained the same in one patient, and increased to 106%, 109%, 113%, and 125% of its initial value in four patients. Overall, the total carnitine level did not change significantly after a 3-year period of TPN (*t* test for paired observation). Free fatty acid and triglyceride levels were not statistically different from control values and remained identical at 3 years when compared with baseline values (Table). The mean cholesterol level was slightly decreased in comparison with control values (p <0.05) but remained within the normal range. The ALT and AST activities, which were slightly increased at initiation of the study, remained unchanged at the study conclusion (Table). No subject had further impairment of liver function. Serum bilirubin levels remained normal throughout the study.

No significant correlation was obtained, either at study initiation or 3 years later, between total or free carnitine and subject age, TPN duration, percentage of calories derived from fat, total amount of infused lipid, plasma free fatty acid value, total serum cholesterol value, or ALT, AST, or alkaline phosphatase activity.

DISCUSSION

The cause of the low plasma carnitine values in this population is unclear. The plasma carnitine concentration at any particular moment is the summation of several metabolic processes, including carnitine intake, synthesis, and excretion.[2] We have previously shown that the plasma lysine and methionine concentrations in children receiving TPN did not differ from those of healthy age-matched control subjects.[3] However, because parenterally administered methionine may be metabolized by a pathway other than transsulfuration, a normal plasma methionine concentration does not necessarily indicate that sufficient substrate is available. It is also conceivable that the subjects absorb enough lysine and methionine or even carnitine to maintain reasonable blood concentrations. A defect of synthesis cannot be attributable to a lack of one of the three vitamins required,[1] ascorbate, niacin, and vitamin B_6, because the levels and vitamin intake were normal in our subjects.[4] In addition, Olson and Rebouche[5] showed that γ-butyrobetaine hydroxylase, the enzyme catalyzing the final step in the carnitine biosynthesis pathway, is not rate limiting for carnitine synthesis, so a lack of carnitine production, if sufficient substrate was available, may not explain the low carnitine levels observed. Schmidt-Sommerfeld et al.[6] showed that carnitine excretion in children receiving TPN is closely correlated with plasma free carnitine concentrations; they concluded that free carnitine and short-chain acylcarnitine are conserved by the kidney in "nutritional" carnitine deficiency. Therefore, although we did not measure the urinary carnitine level, excessive carnitine excretion should not explain the decreased plasma carnitine values. We speculate that low carnitine intake or lack of substrate availability might explain this low plasma carnitine level.

Because plasma is readily accessible, it is frequently used for assessment of carnitine status even though plasma carnitine concentrations do not always correlate with carnitine concentrations in tissue, such as muscle or liver. We did not perform muscle or liver biopsies in our subjects because they were clinically stable. It is unclear whether the low plasma carnitine levels reflect suboptimal levels of tissue carnitine. We could identify no functional significance of low plasma carnitine levels, but given the relatively low lipid intake of the subjects, the finding of normal serum levels of free fatty acids and triglycerides 6 hours after infusion of fat emulsions does not necessarily indicate that the low plasma carnitine concentrations did not affect lipid metabolism. In studies in neonates[7] and infants,[8, 9] carnitine supplementation enhanced lipid utilization, probably because endogenous carnitine synthesis is insufficient in newborn infants.[9] To our knowledge, no study has shown a beneficial effect of carnitine supplementation on lipid metabolism[10, 11] in older children and adults receiving carnitine-free TPN.

We failed to detect a correlation between the low carnitine level and hepatic dysfunction as indicated by elevation of transaminase values. No further increase in the aminotransferase activities occurred during a 3-year period, and there was no hepatomegaly, which could have indicated increased steatosis in the absence of a change in the plasma carnitine value. Bowyer et al.[12] failed to show improvement in abnormal liver function and steatosis in adult TPN patients when they were given supplements of carnitine intravenously in spite of the normalization of plasma and hepatic carnitine levels. To our knowledge, a sole case report exists in which an adult patient receiving long-term TPN had improved liver function after carnitine administration.[13]

The low plasma carnitine values in children receiving long-term TPN and their relatively low fat intake appear to be without clinical consequence even after 10 years of carnitine-free TPN. However, it is possible that plasma free carnitine levels must be very low for an extended period, or that lipid intake must be greater than was the case in this study, before tissue effects are observed. Further studies are needed before carnitine can be established as a conditionally essential nutrient in this population.

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CORRECTIONS

In the article "Controlled Trial of a Single Dose of Synthetic Surfactant at Birth in Premature Infants Weighing 500 to 699 Grams," by Stevenson et al., which appeared in the February 1992 supplement to THE JOURNAL:

—On page S3, the footnote under column 2 should read, "In addition, **four members** of the American Exosurf Neonatal Study Group II participated: David Easa, MD, Kapiolani Medical Center, University of Hawaii, Honolulu, Hawaii; Arun Pramanik, MD, Louisiana State University Medical Center, Shreveport, Louisiana; Ramasubbareddy Dhanireddy, MD, Georgetown University Hospital, Washington, D.C.; and Larry Cook, MD, Kosair Children's Hospital, University of Louisville, Louisville, Kentucky."

—On page S11, the following sentences should have appeared at the end of the first paragraph in column 1: "Of the deaths categorized as 'other,' extreme prematurity/pulmonary immaturity was the most common cause of death in both groups. The deaths of two Exosurf Neonatal–treated infants were attributed to pulmonary hemorrhage."

—On page S11, at the end of the first paragraph in column 2, the sentence printed **"No infant** in this study died of pulmonary hemorrhage" should read as follows: **"Two Exosurf Neonatal–treated infants** in this study died of pulmonary hemorrhage."

In the article "Pulmonary Hemorrhage in Premature Infants After Treatment With Synthetic Surfactant: An Autopsy Evaluation," by van Houten, et al., which appeared in the February 1992 supplement to THE JOURNAL:

—On page S41, in column 1, the second sentence of the second paragraph of METHODS should read, "For the diagnosis of pulmonary hemorrhage, the protocol did **not** require clinical deterioration or appearance of new densities on the chest radiograph."

—On page S42, in column 1, the second sentence of the footnotes for Table III should read, "*Significant increase compared with patients without pulmonary hemorrhage at autopsy, $p < 0.05$."