Carnitine deficiency in premature infants receiving total parenteral nutrition: Effect of L-carnitine supplementation

To investigate whether L-carnitine supplementation may correct nutritional carnitine deficiency and associated metabolic disturbances in premature infants receiving total parenteral nutrition, an intravenous fat tolerance test (1 gm/kg Intralipid over four hours) was performed in 29 premature infants 6 to 10 days of age (15 receiving carnitine supplement 10 mg/kg · day L-carnitine IV, and 14 receiving no supplement). Total carnitine plasma values were normal or slightly elevated in supplemented but decreased in nonsupplemented infants. In both groups, fat infusion resulted in an increase in plasma concentrations of triglycerides, free fatty acids, D-β-hydroxybutyrate, and short-chain and long-chain acylcarnitine, but total carnitine values did not change. After fat infusion, the free fatty acids/D-β-hydroxybutyrate ratios were lower and the increase of acylcarnitine greater in supplemented infants of 29 to 33 weeks' gestation than in nonsupplemented infants of the same gestational age. This study provides evidence that premature infants of <34 weeks' gestation requiring total parenteral nutrition develop nutritional carnitine deficiency with impaired fatty acid oxidation and ketogenesis. Carnitine supplementation improves this metabolic disturbance. (J PEDIATR 102:931, 1983)

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CARNITINE plays a key role in the oxidation of fatty acids by facilitating their transport across the mitochondrial membrane.[1] Its availability may be crucial in the neonatal period, when energy requirements are increasingly met by endogenous and exogenous fat. Carnitine is synthesized in the adult and therefore not considered an essential nutrient. However, the newborn infant may not be capable of substantial carnitine synthesis and thus may be dependent on nutritional carnitine sources. Carnitine is present in human milk and in cow milk formulas[2,3] but not in currently available infusion solutions. Premature infants receiving carnitine-free total parenteral nutrition are at risk to develop carnitine deficiency, with decreased blood[4,5,6] and tissue[7] concentrations. Moreover, decreased carnitine intake may lead to impaired fatty acid oxidation and ketogenesis after fat infusion.[8] We investigated whether the inclusion of L-carnitine in the parenteral nutrition regimen may correct low carnitine concentrations and associated disturbances in fat metabolism.

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AC	Acylcarnitine (esterified carnitine)
BOB	D-β-Hydroxybutyrate
FC	Free carnitine
FFA	Free fatty acids
TC	Total carnitine
TG	Triglycerides
TPN	Total parenteral nutrition

PATIENTS

Twenty-nine appropriate-for-gestational-age premature newborn infants (29 to 37 weeks' gestation, 1200 to 2490 gm birth weight) requiring TPN because of intolerance of feedings given orally were included in the study. Diagnoses included hyaline membrane disease, transient tachypnea of the newborn, meconium aspiration, patent ductus arteriosus, and meconium plug. Infants with marked hyperbilirubinemia, severe central nervous system hemorrhage, sepsis, or metabolic disturbances were excluded from the study.

The project was approved by the Ethical Commission of

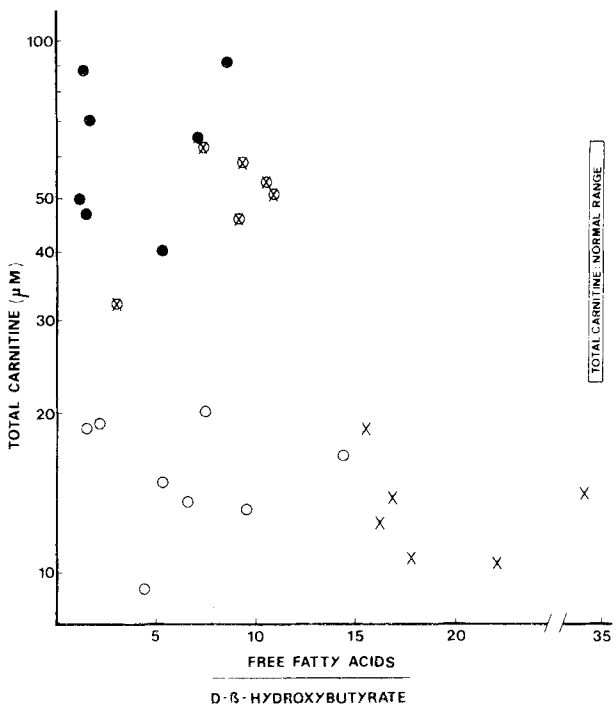

Figure. Relationship between TC plasma values before and FFA/BOB ratios after fat infusion in four groups of premature infants receiving TPN. ●, Carnitine supplemented (34 to 37 weeks' gestation); ○, nonsupplemented (34 to 37 weeks' gestation); ⊗, carnitine supplemented (29 to 33 weeks' gestation); x, nonsupplemented (29 to 33 weeks' gestation).

the Justus Liebig University, Giessen. Informed parental consent was obtained prior to entry into the study.

METHODS

Parenteral nutrition consisted of glucose, amino acids (Aminoplasmal paed), fat (Intralipid), electrolytes, and vitamins. Starting on the second day of life, 15 infants received L-carnitine* (10 mg/kg body weight IV daily) with their parenteral nutrition over approximately 5 hours. The dosage was calculated on the basis of estimated maximal oral carnitine intake of healthy premature infants. No adverse side effects of carnitine supplementation were observed. The remaining 14 infants (controls) received the customary carnitine-free parenteral nutrition without carnitine supplementation. The mean duration of TPN was 5.9 ± 1.3 days in the group receiving carnitine supplementation and 5.6 ± 0.9 days in the control group. There were no differences in clinical condition or nutritional regimen between the two randomly chosen groups. All infants were kept in a thermoneutral environment (incubator) and were in stable clinical condition at the time of an intravenous fat tolerance test performed on the sixth to tenth day of life, before the onset of feedings orally.

*L-Carnitine was a gift from Sigma-Tau Co., Rome, Italy.

Table I. Relationship between carnitine and measurements of lipid metabolism after fat infusion in 28 premature infants (29 to 37 weeks gestation) receiving TPN

	Correlation coefficient r	*Confidence limits P*
TC vs AC	0.81	< 0.001
TC vs BOB	0.40	< 0.05
TC vs FFA	0.14	NS
TC vs FFA/BOB*	0.71	< 0.001
AC vs BOB	0.69	< 0.001
Short-chain AC vs BOB	0.65	< 0.02
Long-chain AC vs BOB	0.78	< 0.001

NS, Not significant.
*Infants of 29 to 33 weeks' gestation only (n = 13).

Heparinized venous blood samples were collected before and at the end of a four-hour continuous infusion of 10 ml/kg 10% Intralipid delivered by infusion pump (B. Braun Perfusor ED 1-300). No other intravenous solution or medication was given during this four-hour period. No carnitine was given on the day of the test. Blood glucose values were closely monitored. All infants remained normoglycemic during the entire test period, with the exception of one infant who developed hypoglycemia (<30 mg/dl). The test was interrupted and the infant was not included in the study population.

The blood specimens were immediately placed on ice, centrifuged, and the plasma stored frozen at −30° C until analysis. Total carnitine and free carnitine were determined by an enzymatic radiochemical method[9] as previously described.[10] Acylcarnitine was considered to be the difference between TC and FC. β-OH-Butyrate was measured by the enzymatic fluorimetric method of Persson[11]; free fatty acids by the method of Novak[12]; and triglycerides, after Dole extraction,[13] by the method of Kreutz.[14] In 14 cases, long-chain AC was measured after perchloric acid precipitation using the method of Brass and Hoppel.[15] Short-chain AC was calculated by subtracting FC and long-chain AC from TC.

Statistical analysis was performed by the Wilcoxon signed-ranks test and by regression analysis with determination of the correlation coefficient and probability.

RESULTS

Effect of fat infusion. In both carnitine-supplemented and nonsupplemented infants, fat infusion resulted in an increase ($P < 0.01$) in plasma concentrations of TG, FFA, BOB, and AC and a decrease of FC ($P < 0.01$), but no

Table II. Measurements of carnitine and lipid metabolism after fat infusion in four groups of premature infants receiving TPN with (+ carnitine) or without (control) L-carnitine

	29 to 33 Weeks gestation		*34 to 37 Weeks gestation*	
	+ Carnitine	*Control*	*+ Carnitine*	*Control*
	n = 7	*n = 6*	*n = 7*	*n = 8*
TC* (μM)	51.5 ± 11.2†	13.2 ± 3.0	65.1 ± 19.7‡	15.6 ± 3.6
AC (μM)	18.1 ± 10.3†	4.9 ± 1.4‡	24.3 ± 13.8‡	8.2 ± 3.0
BOB (mM)	0.20 ± 0.12	0.09 ± 0.07§	0.36 ± 0.22	0.2 ± 0.13
FFA (mM)	1.42 ± 0.73	1.69 ± 1.12	0.89 ± 0.36	1.04 ± 0.33
FFA/BOB	8.3 ± 2.8‖	20.6 ± 7.1‡	3.9 ± 3.2	6.4 ± 4.1
TG (mg/dl)	327.0 ± 205.0	358.0 ± 139.0	307.0 ± 173.0	224.0 ± 121.0

Values are mean ± SD.
*Before fat infusion.
†$P < 0.01$ compared with control 29 to 33 weeks.
‡$P < 0.01$ compared with control 34 to 37 weeks.
§$P < 0.05$ compared with control 34 to 37 weeks.
‖$P < 0.02$ compared with + carnitine 34 to 37 weeks.

change in TC values. Both carnitine ester fractions, short-chain and long-chain AC, increased ($P < 0.01$). Long-chain AC constituted 21 ± 7% of the carnitine esters (AC) after fat infusion.

The correlation among carnitine and various measurements of lipid metabolism after fat infusion are summarized in Table I. BOB values were positively correlated with AC, short-chain AC and long-chain AC; BOB and AC values were positively correlated with preinfusion TC levels. A strong negative correlation between TC plasma values and the calculated FFA/BOB ratios after fat infusion was found in infants of 29 to 33 weeks' gestation. On the basis of the latter finding, the carnitine-supplemented and nonsupplemented (control) groups were subdivided according to gestational age.

Effect of carnitine supplementation. Total carnitine plasma values were normal (25 to 70 μM) or slightly elevated in supplemented infants, but decreased in nonsupplemented infants (Table II). Supplemented infants had higher AC values before and after fat infusion than did nonsupplemented infants. The increase of AC after fat infusion (ΔAC) was 6.9 ± 5.1 nmole/ml in carnitine-supplemented infants of 29 to 33 weeks' gestation and 1.8 ± 1.2 nmole/ml in control infants of the same gestational age range ($P < 0.01$). This difference in ΔAC was not found in the more mature infants.

The BOB values of the less mature control group were lower than those of the more mature control group. β-Hydroxybutyrate and FFA values in the supplemented groups did not differ significantly from those in the nonsupplemented groups of the same gestational age range. However, the FFA/BOB ratios after fat infusion were significantly higher in nonsupplemented infants of 29 to 33 weeks' gestation than in the other three groups (Figure). There were no differences in the FFA/BOB ratios between supplemented and nonsupplemented infants of 34 to 37 weeks' gestation. Among supplemented infants, the less mature group showed slightly but significantly higher FFA/BOB ratios than the more mature group.

One infant, of 32 weeks' gestation, had a subnormal TC plasma value (20.3 μM) despite carnitine supplementation and had an FFA/BOB ratio of 17. Abnormally high carnitine excretion and hyperaminoaciduria were documented. Therefore, this patient was not included in the statistical evaluation of the data.

Triglyceride values after fat infusion did not differ among the four groups.

DISCUSSION

It is evident from our data and from earlier studies[5, 8] that premature infants receiving TPN have decreased TC plasma concentrations. Intravenous L-carnitine supplementation can maintain normal TC plasma values. Preliminary pharmacokinetic studies demonstrated that L-carnitine has a half-life of 115 to 120 minutes in the plasma of premature infants (unpublished data), so TC concentrations measured more than 12 hours after the last carnitine dose can be regarded as basal carnitine values.

In agreement with our earlier study,[8] the proportion of AC to FC (AC/FC ratio) increased after fat infusion, indicating elevated fatty acid oxidation. In addition, an increase of both long-chain AC and short-chain AC after fat infusion was found. This parallel increase of both carnitine ester fractions in plasma has been demonstrated under other conditions of accelerated fat metabolism, for example, fasting[16] or diabetic ketoacidosis.[17] The positive correlations between BOB and both long-chain AC and short-chain AC after fat infusion are in agreement with the

concept that the release of carnitine esters into the blood is directly related to the rate of ketogenesis in the liver.[18]

We were also able to confirm our previous finding that AC and BOB values after fat infusion are positively correlated with TC concentrations. If carnitine plasma values reflect carnitine liver content, carnitine may be a limiting factor in hepatic fatty acid oxidation and ketogenesis in premature infants receiving TPN.

The FFA/BOB ratio in plasma (increased when ketogenesis is impaired) may reflect the liver's capacity to oxidize fatty acids; it is elevated after fasting in systemic carnitine deficiency.[19, 20] This ratio is apparently affected by at least two factors: gestational age and TC concentrations. It was higher in infants of 29 to 33 weeks' gestation than in the more mature infants, despite similar TC values. This gestational age–related difference was less pronounced in the carnitine-supplemented than in the control infants. Infants of 29 to 33 weeks' gestation receiving carnitine supplementation had clearly lower FFA/BOB ratios after fat infusion than did nonsupplemented infants of the same gestational age range, indicating that the ability to oxidize fatty acids was improved by carnitine supplementation. The greater increase of AC after fat infusion in these infants may be yet another indicator of improved fatty acid oxidation.

The explanation of our findings remains speculative. A reduction of liver carnitine concentration has been shown to occur in premature infants receiving TPN.[7] Although the concentration of carnitine in the liver necessary for optimal fatty acid oxidation and ketogenesis is unknown, the degree of liver carnitine reduction in very immature infants may be large enough to cause impairment of fatty acid oxidation. Moreover, the activity of carnitine palmitoyl transferase has been shown to be influenced by gestational age[2] and carnitine intake.[21]

Triglyceride plasma concentrations achieved after fat infusion were highly variable. This finding is in agreement with the wide range of postheparin lipoprotein lipase activity in premature infants of >26 weeks' gestation.[22] There was no significant difference in triglyceride values among our four patient groups, indicating that the rate of lipolysis was neither related to gestational age nor to carnitine supply.

We provide evidence that premature infants of <34 weeks' gestation requiring TPN for five to nine days exhibit impaired fatty acid oxidation and ketogenesis related to nutritional carnitine deficiency. This metabolic disturbance was demonstrated under conditions of increased fat catabolism induced by a fat tolerance test. It may not be evident during the common practice of infusing fat at slower rates simultaneously with glucose. However, our findings suggest that carnitine supplementation improves the ability of these immature infants to oxidize fatty acids. Further investigations are required to determine whether it represents a clinically significant contribution to their parenteral nutrition.

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Clinical and laboratory observations

Iodine-induced alterations of thyroid function in newborn infants after prenatal and perinatal exposure to povidone iodine

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CRITICAL EVALUATION of the TSH screening data obtained in West Berlin since 1978 discloses a tenfold higher incidence of TSH elevations (>20 μU/ml) in one department of obstetrics, compared with the incidence in all other hospitals in Berlin. Further investigations reveal that povidone-iodine solutions were used exclusively in this department as a topical germicide during all deliveries, especially in mothers with premature rupture of membranes.[1]

Large quantities of iodine transiently inhibit biosynthesis and secretion of thyroid hormones if a certain threshold of iodine is reached in the serum and the thyroid gland.[2] Transient hypothyroidism or goiter was observed in newborn infants after topical application of povidone-iodine or iodine-containing alcoholic solutions.[3] The aim of our study was to demonstrate whether the observed TSH elevations were caused by an increased absorption of iodine and indicate transient thyroid dysfunction.

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MATERIALS AND METHODS

A prospective study was performed in 66 mothers and their newborn infants perinatally exposed to povidone-iodine as well as in a control group of 18 mothers and their infants in another hospital who were not exposed to iodine. For disinfection during labor and delivery, a plastic catheter was attached to the scalp electrode for fetal heart rate monitoring and a 2% solution of povidone-iodine was pumped through with a velocity of approximately 6 ml/min in cases of premature rupture of the membranes, a catheter was inserted to the portio with a ring pessary, and continuous rinsing with 1% povidone-iodine solution was continued to delivery[1]; the duration of treatment varied from 5 to 30 hours, with a median of 17 hours. Blood samples were collected from the mothers approximately two hours before delivery and on the third and fifth day after delivery. In the newborn infants the first blood sample was taken from the umbilical cord. Further blood samples were collected on days 3 and 5 by venipuncture,