Effects of parenteral L-carnitine supplementation on fat metabolism and nutrition in premature neonates

Cynthia M. Bonner, MD, Karan L. DeBrie, RD, George Hug, MD, Evelyn Landrigan, BS, and Bonnie J. Taylor, MD

From the Department of Pediatrics, University of Arkansas for Medical Sciences, and Arkansas Children's Hospital, Little Rock, and the Department of Pediatrics, University of Cincinnati, and Division of Enzymology, Children's Hospital Medical Center, Cincinnati, Ohio

The effects of parenteral L-carnitine supplementation on fat metabolism, nutrient intake, and plasma and erythrocyte carnitine concentrations were studied in 43 very low birth weight infants. Infants were randomly assigned to control or carnitine-supplemented (50 μmol/kg per day) groups within two weight categories: group 1, 750 to 1000 gm, and group 2, 1001 to 1500 gm. Plasma total, free, and acyl carnitine levels, erythrocyte carnitine levels, serum β-hydroxybutyrate and triglyceride levels, and total fat intake were monitored weekly until 50% of total caloric intake was met enterally. Neonates receiving carnitine had higher plasma carnitine levels than control groups (total carnitine: group 1, 75.2 ± 22.9 vs 9.6 ± 2.7 mmol/ml; group 2, 61.6 ± 31.2 vs 13.0 ± 9.2 nmol/ml). Levels of β-OH-butyrate decreased from baseline in control neonates (group 1, 0.12 ± 0.06 to 0.03 ± 0.02 mmol/L; group 2, 0.11 ± 0.03 to 0.05 ± 0.02 mmol/L); they remained unchanged in supplemented groups. Thus ketogenesis appeared less impaired in infants receiving supplements. Supplemented group 2 tolerated more fat than control group 2; triglyceride levels remained acceptable in all groups. Carnitine group 2 had greater weight gain than control group 2 during the first 2 weeks of life. We conclude that very low birth weight infants requiring prolonged parenteral nutrition have carnitine deficiency with impaired ketogenesis. Parenteral administration of carnitine appears to alleviate this metabolic disturbance. (J Pediatr 1995;126:287-92)

Premature infants have limited fat stores and often require parenteral nutrition for extended periods. Parenteral nutrition includes emulsified lipids to supply calories for growth and essential fatty acids. Carnitine, β-hydroxy-γ-trimethylaminobutyric acid, facilitates transport of fatty acids across the inner mitochondrial membranes through an acyltransferase enzyme system[1, 2] and is required in fatty acid metabolism. Neonates have limited free fatty acid oxidative capacity, which may relate to their low acylcarnitine and free carnitine levels.[3-6] Carnitine is synthesized in human liver and kidney[7] from the essential amino acids lysine and methionine.[8] Previous studies have shown that neonates receiving parenteral nutrition devoid of carnitine are unable to synthesize sufficient carnitine to maintain plasma concentrations equivalent to values found in healthy newborn infants, older children, or adults,[3, 4, 6, 9-11] despite the presence of these amino acids in parenteral nutrition fluids. Therefore infants must rely on dietary intake of carnitine to maintain adequate carnitine stores.

Depletion of tissue carnitine stores has been reported in neonates who received parenteral nutrition devoid of carnitine for at least 15 days.[12] Studies evaluating carnitine supplementation have yielded varying results regarding fat

Submitted for publication April 5, 1994; accepted Aug. 17, 1994.

Reprint requests: Cindy Bonner, MD, Department of Pediatrics, Arkansas Children's Hospital, 800 Marshall St., Little Rock, AR 72202.

0022-3476/95/$3.00 + 0 9/23/60000

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metabolism. Some have reported enhanced ketogenesis,[9, 13] whereas others have demonstrated no effect.[14, 15] There have been no reported studies of carnitine supplementation and its effect on fat metabolism during the slower, more prolonged fat infusion that is normally used in intensive care nurseries, as opposed to evaluation during a fat tolerance test. We prospectively investigated the changes in carnitine status and fat metabolism of very low birth weight infants receiving intravenous infusions of L-carnitine.

METHODS

Patients. Forty-three premature neonates admitted to the Arkansas Children's Hospital Neonatal Intensive Care Unit at less than 48 hours of age were studied. The study was approved by the University of Arkansas for Medical Sciences Institutional Review Board. The statistical basis for determining the specific numbers of patients to be enrolled was a power analysis with a detectable difference of 40% to 50% and an anticipated standard deviation of 25% to 30% in the measurements.[16] Given those requirements, each group would have had to contain from 4 to 16 patients. Ten patients were then chosen as the sample size for each group on the basis of an anticipated enrollment during 1 year. Informed consent was obtained from a parent or guardian before enrollment into the study. The infants were classified into weight groups according to their birth weight (group 1, 751 to 1000 gm; group 2, 1001 to 1500 gm) and then were randomly assigned to receive either intravenous infusions of L-carnitine (50 μmol/kg per day) or no supplementation within their respective weight category. Eligible infants who were not enrolled included five infants whose disease was so severe that they were not expected to survive >48 hours, four infants who had received erythrocyte transfusions before initial laboratory studies were obtained, and two infants who were not expected to receive parenteral nutrition for more than 1 week. The study was not masked so that safety of the parenteral form of carnitine, which was not licensed by the U.S. Food and Drug Administration at the time of this study, could be followed more closely. Patient characteristics were recorded, including birth weight, sex, estimated gestational age by Dubowitz[17] examination, weight gain during study, the duration of enrollment in the study until 50% caloric intake (60 kcal/kg per day) was met enterally with human milk or a carnitine-containing formula, and duration of hospitalization. A clinical severity score,[18] which summarizes the severity of a patient's clinical illness, also was used to ensure group equality. Daily intake and output records were maintained.

Nutritional regimens. Patients received parenteral nutrition beginning on postnatal day 2 or 3; on the next day, intravenous infusion of lipid emulsion (Intralipid; Kabi Pharmacia, Clayton, N.C.), given continuously for 20 to 24 hours, was begun. Lipid intake was started at 0.5 to 1.0 gm/kg per day and advanced by 0.25 to 0.5 gm/kg per day. Lipid intake was not advanced if the serum triglyceride concentrations were ≥1.7 mmol/L (150 mg/dl), but was not decreased if the serum triglyceride level was <2.25 mmol/L (200 mg/dl). Serum triglyceride values were monitored daily while intravenous infusion of lipids was advanced to a maximum of 3.0 gm/kg per day and then monitored weekly. The patients who had been randomly assigned to the carnitine groups received L-carnitine, 50 μmol/kg per day, as a continuous infusion beginning at the institution of parenteral nutrition. At the neonatologist's discretion, enteral feedings were begun when the clinical condition was deemed stable, and were advanced in volume and concentration as tolerated.

Laboratory studies. On admission to the hospital, and then weekly as long as the patient remained enrolled in the study, blood was obtained for carnitine levels (plasma total, free, and acyl carnitine, and erythrocyte carnitine), serum ketone (β-OH butyrate) levels, and serum triglyceride concentrations. Blood was collected in heparinized tubes and immediately placed on ice, and then the plasma was separated by centrifugation. Aliquots of plasma were immediately frozen (plasma carnitine and β-OH-butyrate). Carnitine levels were assayed according to the Cederblad-Lindstedt method.[19] Triglycerides were measured by an enzymatic assay with correction for free glycerol.[20] Ketone bodies were determined by spectrophotometric enzymatic assays.[21] All reported laboratory measurements were performed in the same laboratory (carnitine in the Cincinnati Children's Hospital Medical Center Division of Enzymology; lipid indexes at Arkansas Children's Hospital). Routine biochemical and hematologic tests were done as a part of our usual clinical monitoring. Two-week values are reported here because previous work has shown tissue carnitine levels to be decreased after at least 2 weeks of parenteral nutrition devoid of carnitine.[12]

Statistical analysis. Mann-Whitney U tests[22] were performed to determine whether differences existed in means between and within groups for patient characteristics, nutrient intake, lipid indexes (β-OH-butyrate and triglyceride), and carnitine levels. Statistical significance was established at $p < 0.05$.

RESULTS

There was no significant difference for any demographic variable between carnitine and control groups within each weight category. Diagnoses and clinical severity scores were similar within and between groups. There were no documented cases of sepsis or other infections. Nutrient intake of each group was similar (Table I), with the exception of fat intake in group 2. There was no difference in the

Table I. Average daily nutrient intake of very low birth weight infants during first 2 weeks of life

	Group 1 (751-1000 gm)		Group 2 (1001-1500 gm)	
	Control	Carnitine	Control	Carnitine
Calories (kcal/kg/day)	74 ± 14	71 ± 10	67 ± 9	72 ± 8
Protein (gm/kg/day)	2.1 ± 0.3	1.8 ± 0.6	1.7 ± 0.4	1.9 ± 0.2
Fat (gm/kg/day)	2.3 ± 0.5	2.1 ± 0.4	2.0 ± 0.6	2.5 ± 0.4*

Values are expressed as mean ± SD. Nutrient intake represents combined parenteral and enteral intake.
*p <0.05, compared with control values

Table II. Fractionated carnitine levels of very low birth weight infants on parenteral nutrition regimen with or without intravenous carnitine supplementation

Duration of regimen, by group	Free (nmol/ml)	SC (nmol/ml)	RBC total (nmol/mgh)
Child normal values*	(43.5 ± 13.3)	(15.4 ± 9.1)	(NA)
Group 1, control (n = 11)			
Initial	20.0 ± 12.5	7.9 ± 2.7	0.17 ± 0.06
After 2 wk	5.8 ± 2.0[b]	3.7 ± 1.5[b]	0.05 ± 0.02[b]
Group 1, carnitine (n = 11)			
Initial	17.3 ± 8.8	5.3 ± 2.4	0.18 ± 0.06
After 2 wk	56.8 ± 19.5[b,d]	18.4 ± 6.5[b,d]	0.07 ± 0.05[b]
Group 2, control (n = 10)			
Initial	18.0 ± 8.7	5.6 ± 3.3	0.13 ± 0.06
After 2 wk	8.7 ± 6.4[b]	4.1 ± 3.0	0.04 ± 0.02[b]
Group 2, carnitine (n = 11)			
Initial	17.0 ± 8.7	4.9 ± 2.7	0.14 ± 0.07
After 2 wk	50.1 ± 23.9[a,d]	14.1 ± 4.9[a,d]	0.10 ± 0.06[c]

Values are expressed as mean ± SD.
SC, Short chain; *RBC*, red blood cells; *mgh*, milligrams of hemoglobin; *NA*, not available.
*Normal values were established in the reference laboratory where assays were performed.
[a]p <0.05 from baseline.
[b]p <0.01 from baseline.
[c]p <0.01 from control.
[d]p <0.001 from control.

percentage of nutrient intake provided enterally when carnitine-supplemented infants were compared with control infants within each weight category.

On entering the study, all infants had carnitine levels that were 50% below the published normal values for children and adults, but were similar to values reported previously for premature infants.[23] Plasma total carnitine levels decreased from their low baseline to 20% to 25% of normal in both control groups (p <0.01), and rose to within the normal range in both carnitine groups (p <0.05; Fig. 1). Plasma carnitine levels were significantly higher in the infants given carnitine than in the control infants of the same weight classification after 2 weeks of parenteral nutrition (p <0.001). Erythrocyte carnitine levels decreased in both control groups and in the smaller infants given carnitine (group 1). However, the larger infants receiving carnitine (group 2) had a significantly higher erythrocyte carnitine level than control group 2 after at least 2 weeks on a parenteral nutrition regimen (p <0.01; Table II). The plasma carnitine levels in the control infants in each weight classification rose significantly once enteral feedings were established (Table III). Levels of β-OH-butyrate decreased significantly from baseline in both control groups (p <0.05),

Table III. Total carnitine values of control very low birth weight infants on parenteral nutrition regimen before and after institution of enteral feeding

Group	Duration of enteral nutrition	Total carnitine (nmol/ml)	Enteral intake (%)
Group 1 (n = 11)	Initial	7.3 ± 4.5	
	1 Wk	12.2 ± 5.9*	38 ± 12
	2 Wk	37.2 ± 39.6*	78 ± 26
Group 2 (n = 10)	Initial	10.8 ± 7.2	
	1 Wk	14.9 ± 9.3*	43 ± 16
	2 Wk	25.7 ± 13.3*	82 ± 22

Values are expressed as mean ± SD.
*p <0.05 from baseline.

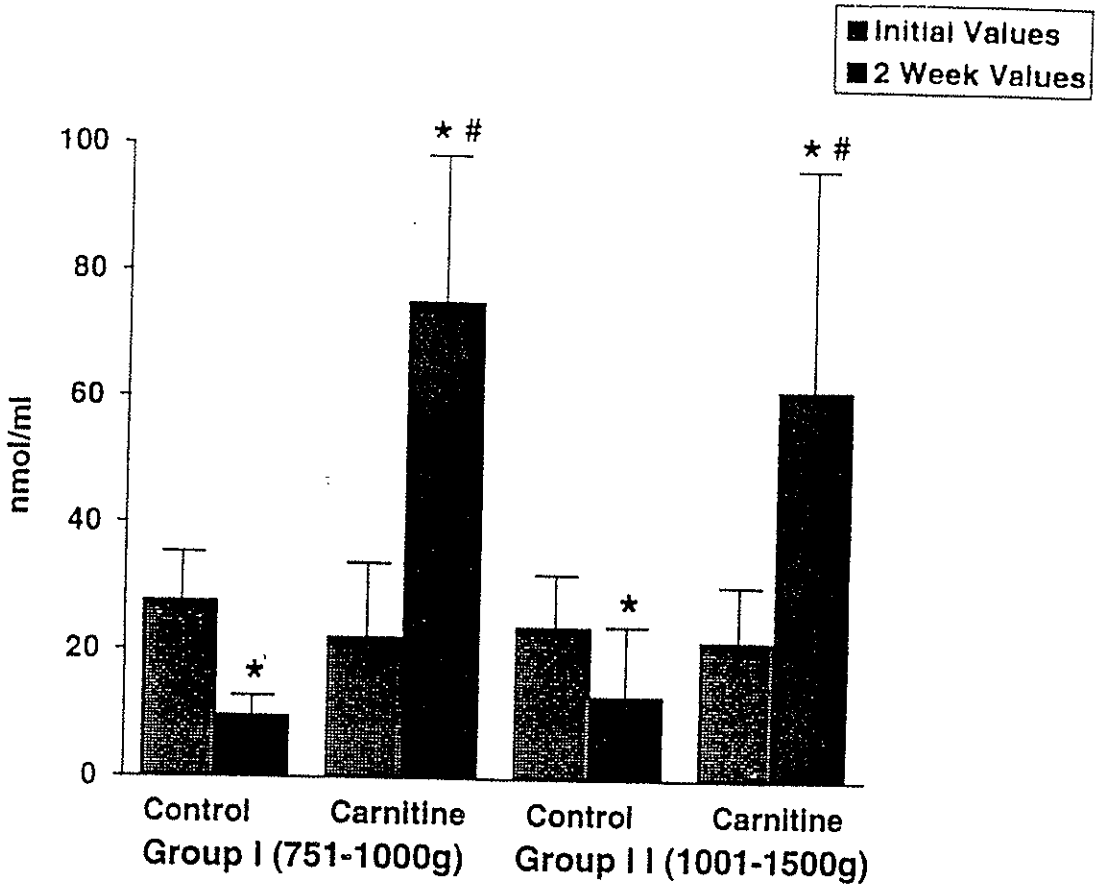

Fig. 1. Total carnitine levels (in nanomoles per milliliter; mean ± SD) of very low birth weight infants receiving parenteral nutrition with or without intravenous carnitine supplementation. In group 1: control n = 11, carnitine n = 11; in group 2, control n = 10, carnitine n = 11. Values at entry to the study (initial) are shown as *shaded bars*. Values after 2 weeks of parenterally administered nutrition with or without carnitine supplementation (2 weeks) are shown as *dark solid bars*. *p <0.05 from baseline; #p <0.001 from control.

and remained unchanged in both carnitine groups (Fig. 2). Carnitine group 2 tolerated significantly more lipid than control group 2 during the study period (p <0.05; Table I). The serum triglyceride level remained acceptable regardless of group or supplementation status. Carnitine group 2 had a significantly greater weight gain per day (6.9 ± 5.9 vs 1.3 ± 7.1 gm/day) than control infants in this weight category during the first 2 weeks of life (p <0.05).

DISCUSSION

We have demonstrated, as have others,[3-6, 9-11, 13] that maintenance of plasma carnitine levels is dependent on an exogenous supply of carnitine in the premature neonate. Although neonates requiring prolonged parenteral nutrition receive the essential precursors lysine and methionine[8] for synthesis, plasma carnitine levels fall to levels consistent with systemic carnitine deficiency within 2 weeks and continue to decrease or remain low until carnitine is supplied exogenously. Reduced capacity for biosynthesis of carnitine appears to be secondary to low activities of several enzymes.[24] Plasma carnitine levels increased when feedings with carnitine-containing human milk or premature formula were begun. Neonates who received parenterally administered carnitine had normal plasma carnitine levels within 2 weeks. This dose of carnitine was chosen to correlate with the minimal amount normally found in human milk, and to be comparable to the amount used in previous studies. We evaluated the different fractions of plasma carnitine and found that all fractions were decreased in nonsupplemented infants and rose to within the normal range in supplemented infants.

The erythrocyte carnitine levels at the beginning of our study were slightly lower than previously reported values[25, 26] for preterm neonates, but decreased as previously described[25] with increasing postnatal age. However, carnitine group 2 had no significant decrease in their erythro-

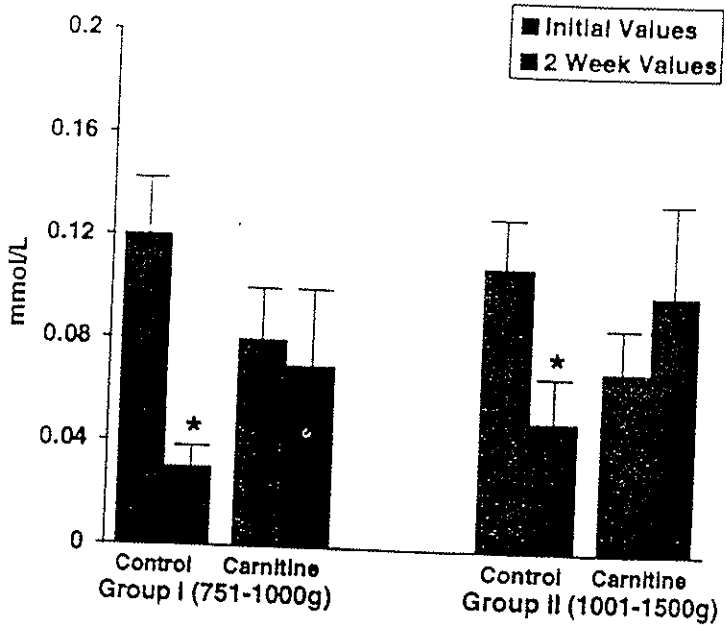

Fig. 2. Levels of β-OH-butyrate (in millimoles per liter; mean ± SEM) of very low birth weight infants receiving parenteral nutrition with or without intravenous carnitine supplementation. In group 1: control n = 11, and carnitine n = 11. In group 2: control n = 10, and carnitine n = 11. Values at entry to the study *(Initial)* are shown as *shaded bars*. Values after 2 weeks of parenterally administered nutrition with or without carnitine supplementation (2 weeks) are shown as *dark solid bars*. *$p < 0.05$ from baseline.

cyte carnitine content during a 2-week period. Erythrocytes may serve a transport function for carnitine.[27] If such a transport system exists, erythrocyte carnitine may be an important indicator of tissue availability of carnitine. If so, these results suggest insufficient tissue stores in our smallest weight group despite supplementation.

We demonstrated that premature neonates receiving parenterally administered nutrition devoid of carnitine had significantly decreased β-OH-butyrate levels, and that parenteral carnitine supplementation resulted in increased levels. Most previous studies investigating fatty acid metabolism with carnitine supplementation used fat tolerance tests[9, 10] to demonstrate effects of carnitine on fat metabolism. We infused the lipid for 20 to 24 hours, the routine schedule for fat administration in our nursery. Perhaps because the lipid was not infused rapidly, β-OH-butyrate levels were twofold to fivefold lower than those reported in other studies.

Carnitine group 2 tolerated significantly more fat than the control subjects in this weight group. There was no difference in the amount of heparin used between the groups in each weight classification. Therefore heparin-induced lipoprotein lipase activity[28] should not have affected the results of triglyceride clearance. Although increased weight gain occurred in the supplemented infants in the larger birth weight group, this finding may not be clinically significant because weight gain during the initial 2 weeks of life was minimal in all groups. The only other study evaluating changes in growth rate in very low birth weight infants revealed an increase in growth only after increasing the dose of parenterally administered L-carnitine to 100 μmol/kg per day.[10] No adverse side effects of carnitine supplementation, such as diarrhea or foul odor, which have been reported with oral supplementation,[29] were noted.

In summary, intravenous carnitine supplementation resulted in increased plasma carnitine levels and enhanced ketogenesis in premature infants maintained on a regimen of prolonged parenteral nutrition devoid of carnitine (at least 2 weeks). Our results suggest that preterm neonates have limited carnitine reserves and that parenteral carnitine supplementation may increase these stores. Erythrocyte carnitine, amount of lipid tolerated, and weight gain were improved with parenteral carnitine supplementation at the current dose (50 μmol/kg per day) in the larger premature neonates (>1000 gm). These findings suggest that intravenous carnitine supplementation along with parenterally administered nutrition may allow for more rapid growth and better fat utilization in the larger group of very low birth weight infants. Additional studies are needed in smaller neonates to see whether more pronounced benefits are achieved with larger doses of intravenously administered L-carnitine.

We acknowledge the invaluable technical assistance and advice from the metabolics laboratory at Arkansas Children's Hospital, including Dr. Marge Brewster, Fran Soderberg, and Jan Woodall, and the assistance from the neonatal nursing staff at Arkansas Children's Hospital Neonatal Intensive Care Unit, especially Pam McMillan, RN.

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