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Effect of Intravenous L-Carnitine on Growth Parameters and Fat Metabolism during Parenteral Nutrition in Neonates

RICHARD A. HELMS, PHARM.D.,* ELIZABETH C. MAUER, PHARM.D.,* WILLIAM W. HAY, JR., M.D.,†
MICHAEL L. CHRISTENSEN, PHARM.D.,* AND MICHAEL C. STORM, PH.D.‡

From the Center for Pediatric Pharmacokinetics and Therapeutics at the University of Tennessee and from the Departments of Clinical Pharmacy and Pediatrics at The University of Tennessee, Memphis, Tennessee, The University of Colorado,† Denver, Colorado, and Kendall McGaw Laboratories,‡ Irvine, California*

ABSTRACT. To determine whether intravenous carnitine can improve nutritional indices, neonates requiring parenteral nutrition were randomized into carnitine treatment (n = 23) and control (n = 20) groups. Observed plasma lipid indices, carnitine and nitrogen balances, and plasma carnitine concentrations were not different in the prestudy period. Under standardized, steady-state conditions, 0.5 g/kg Intralipid was administered intravenously over 2 hr prior to carnitine administration, after infants received 7 days of 50 μmol/kg/day, and after a second 7 days of 100 μmol/kg/day of continuous intravenous L-carnitine as part of parenteral nutrition. Triglyceride (TGY), free fatty acid (FFA), acetoacetate (AA), β-hydroxybutyrate (BOB), and plasma carnitine concentrations were measured prior to and at 2, 4, and 6 hr after the initiation of the lipid bolus. Twenty-four-hour urine collections for nitrogen and carnitine balance were obtained on days 7 and 14. Neonates receiving carnitine had significantly greater concentrations of plasma carnitine on days 7 and 14 ($p < 0.001$). Greater nitrogen ($p < 0.05$) and carnitine ($p < 0.001$) balances and weight gain (week 2, $p < 0.05$) were found in the carnitine-supplemented group when compared with controls. On day 14, (BOB + AA)/FFA ratios were significantly higher ($p < 0.05$), and peak TGY concentrations and 6-hr FFA concentrations were significantly lower ($p < 0.05$) in the treatment group. Carnitine supplementation was associated with modest increases in growth and nitrogen accretion possibly by enhancing the neonate's ability to utilize exogenous fat for energy. (*Journal of Parenteral and Enteral Nutrition* **14**:448–453, 1990)

Limited free fatty acid (FFA) oxidative capacity may relate to low acylcarnitine and free carnitine levels in neonates and infants.[1–4] During gestation carnitine is transported to the fetus by the placenta in amounts adequate to support metabolism.[5] In preterm infants, however, plasma carnitine concentrations decrease rapidly during the first 3 postnatal days and continue to fall through 35 days of postnatal life if no exogenous carnitine is given.[6,7] Depletion of tissue stores of carnitine has been demonstrated in newborn infants who received more than 15 days of total parenteral nutrition.[8] Carnitine has been given orally to preterm infants receiving long-term total parenteral nutrition, producing enhanced ketogenesis.[9] Other studies evaluating intravenous carnitine supplementation have resulted in divergent findings; some demonstrated enhanced ketogenesis whereas others demonstrated no effect.[10–12] These divergent findings may have related to methodologic or study population differences. No studies have evaluated growth differences in preterm neonates receiving intravenous carnitine as part of parenteral nutrition.

Therefore, we investigated the effects of intravenous L-carnitine supplementation on plasma carnitine concentrations, carnitine balance, nitrogen balance, weight gain, and fat clearance and utilization in preterm neonates receiving parenteral nutrition.

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Reprint requests: Richard A. Helms, PharmD, Department of Clinical Pharmacy and Pediatrics, 26 South Dunlap, Suite 202, Memphis, TN 38163.

PATIENTS AND METHODS

Patients

Forty-three neonates from three different teaching institutions were studied. The protocol underwent Institutional Review Board approval and parental informed consent was obtained for each subject. Prior to enrollment, all subjects received carnitine-free nutrients and none received drugs known to alter carnitine or lipid metabolism. All neonates required a minimum of 7 to 14 days of parenteral nutrition from time of study enrollment (34 received 14 days, nine received 7 days). Infants were permitted limited enteral intake (less than 15% of total caloric and protein intake) with formulas containing little or no carnitine (Pregestimil, Nutramigen, Portagen; Mead Johnson Nutritional, Evansville, IN).[13] Normal saline without added heparin was used to flush all venous lines throughout the study.

Detailed daily intake and output records were maintained. Routine hematologic and biochemical testing was done as necessary. Weight gain was derived from the slope of a linear regression plot of each patient's daily weight *vs* study day.

Carnitine Supplementation

Patients were randomized by use of a random number table into carnitine treatment and control groups at each institution. The investigators and primary care physicians were blinded regarding the treatment regimen. Only the preparative pharmacist was aware of actual carnitine intake. Carnitine-treated infants received 7 days of continuous intravenous L-carnitine (Kendall

McGaw, Irvine, CA) at a dose of 50 μmol/kg/day (8.1 mg/kg/day) followed by 7 days of 100 μmol/kg/day (16.1 mg/kg/day). Based on a previous study using oral carnitine supplementation, a 50-μmol/kg/day dose resulted in plasma values below normal values.[9] Although no assessment of bioavailability was made in the oral study, we speculated that a higher intravenous dose might be needed to normalize plasma concentrations. Therefore, this study was designed to increase the dose to 100 μmol/kg/day in week 2. Intravenous L-carnitine supplementation was continued until the last observation was made after the final fat bolus. Oral and packed red blood cell (PRBC) carnitine intakes (covert sources of carnitine) were extremely low for both groups (Table I).

Parenteral Nutrition and Fat Infusions

Parenteral nutrition during the study provided 2.1 ± 0.4 g/kg/day of amino acids (FreAmine III, Kendall McGaw), 91 ± 32 mg/kg/day of cysteine HCl (Abbott Laboratories, North Chicago, IL), 15.8 ± 4.7 g/kg/day of dextrose, and 1.8 ± 0.8 g/kg/day of lipid emulsion (Intralipid, Kabi Vitrum, Alameda, CA). Lipid intake was started at 0.5 to 1.0 g/kg/day and increased by 0.25 to 0.5 g/kg/day. Increases in lipid dose were determined by regular assessment of plasma triglyceride (TGY) values (<200 mg/dl) and/or plasma turbidity (nonturbid). Electrolytes, vitamins, minerals, and trace elements were given as appropriate for size and postnatal age. Patients of greater weight (>1200 g) and postnatal age (>2 weeks) received greater total energy intake (90 ± 12 *vs* 73 ± 13 kcal/kg/day) but similar total protein intake (2.3 ± 0.4 *vs* 2.3 ± 0.5 g/kg/day). Randomization resulted in similar nutrient intake, except for intravenous carnitine, for patients in the treatment and control groups. (Table I).

Infants received a lipid infusion of 0.5 g/kg over 2 hr on days 0 (prestudy), 7, and 14 of the study. For 12 to 16 hr prior to this lipid bolus and continuing throughout the postbolus 6-hr sampling period, intravenous lipid infusion or lipid-containing feedings were discontinued. During this 12 to 16 hr, carbohydrate administration from the parenteral nutrition solution was limited to 10–12 g/kg/day of glucose. This was done to achieve a stable insulin output and to optimize the recognition of lipid-induced ketone body production after the 2-hr lipid bolus.

TABLE I
Clinical findings (mean ± SD)

	Control (n = 20)	Treatment (n = 23)	*p* Value
Patient characteristics on entrance			
Sex			
Male	11	12	
Female	9	11	
Gestational age (wk)	31.5 ± 4.2	31.8 ± 4.8	0.839
Postnatal age (wk)	2.7 ± 1.7	2.2 ± 1.0	0.291
Postconceptual age (wk)	34.2 ± 4.2	34.0 ± 4.6	0.888
Weight (kg)	1.52 ± 0.78	1.48 ± 0.60	0.853
Length (cm)	39.1 ± 5.7	39.3 ± 3.8	0.900
Nutrient intake			
Total calories (kcal/kg/day)*			
Wk 1	73 ± 17	80 ± 18	0.161
Wk 2†	80 ± 20	88 ± 18	0.244
Total protein (g/kg/d)*			
Wk 1	2.10 ± 0.53	2.31 ± 0.54	0.204
Wk 2†	2.30 ± 0.47	2.45 ± 0.49	0.373
IV carnitine (mg/kg/day)			
Wk 1	0.06 ± 0.26§	9.44 ± 3.39	<0.001
Wk 2†	0 ± 0	14.90 ± 2.87	<0.001
Oral/PRBC carnitine (mg/kg/day)			
Wk 1	0.03 ± 0.05	0.06 ± 0.12	0.260
Wk 2†	0.06 ± 0.10	0.07 ± 0.09	0.724
Weight gain (g/kg/day)			
Wk 1	13.7 ± 13.4	12.6 ± 13.6	0.781
Wk 2†	6.3 ± 13.5	17.9 ± 12.7	0.026
Nutrient balance (mg/kg/day)‡			
Nitrogen	250 ± 90	300 ± 86	0.027
Carnitine	−0.1 ± 0.2	6.3 ± 3.8	<0.001
Plasma carnitine (nmol/ml)			
Prestudy	12.1 ± 4.8	17.9 ± 8.6	0.089
Day 7	10.6 ± 3.7	68.7 ± 24.4	<0.001
Day 14†	9.4 ± 4.0	87.9 ± 31.0	<0.001

* From parenteral and enteral intake.
† Control, n = 18; treatment, n = 16.
‡ Control, n = 30; treatment, n = 36.
§ Represents the accidental administration of carnitine in one subject for 1 day.

Biochemical Measurements

On days 0, 7, and 14 of the study, blood was collected for plasma carnitine, TGY, FFA, β-hydroxybutyrate (BOB), and acetoacetate (AA) concentrations at 0, 2, 4, and 6 hr from the start of the lipid bolus. Twenty-four-hour urine collections for carnitine and nitrogen excretion were completed prior to initiating supplementation with L-carnitine, and additionally, on days 7 and 14. At least 80% of the total urine output during a 24-hr period was collected for the collection to be declared valid. Nitrogen and carnitine balances were calculated by subtracting total urinary losses from intake and dividing by weight in kilograms. Mean carnitine and nitrogen balances were determined and reported for patients with multiple observations. Fecal output was minimal in all infants; thus, this source of nitrogen loss was ignored.

Blood was collected in heparinized tubes, which were immediately placed on ice, and then the plasma was separated by centrifugation. Aliquots of plasma were either immediately frozen (TGY, FFA, and plasma carnitine) or extracted with 6% perchloric acid to prevent degradation (AA and BOB). TGY was measured by an enzymatic assay with correction for free glycerol.[14] FFA and ketone bodies were determined by microfluorometric enzymatic assays.[15,16] Plasma carnitine and urinary carnitine were measured using a modification of the method originally described by Cederblad and Lindstedt.[17] Total urinary nitrogen was determined using pyrochemiluminescence (Antek Instruments, Houston, TX). All reported laboratory measurements were performed within the same laboratories (lipid indices at Tennessee, carnitine at Florida, and nitrogen at Kendall McGaw).

Statistical Analysis

Student's *t*-tests for unpaired and paired samples were performed to determine whether differences existed in means between and within groups for patient characteristics on entrance to the study and for nutrient intake. Fisher's exact test was used for assessing the difference in sex distribution. Lipid parameters (TGY, FFA, BOB, AA) and total plasma carnitine were analyzed in a nontransformed and logarithmically transformed fashion. In general, logarithmic transformation did not alter the direction or significance of data. The derived parameter (BOB + AA)/FFA was computed to evaluate the relative efficiency of ketone body production from a fixed concentration of FFA. Significance testing between and within groups for plasma lipid parameters and plasma carnitine at 7 and 14 days was conducted using analysis of variance. Since demographic parameters such as gestational age and postnatal age may influence weight gain and nitrogen balance, postconceptual age (gestational age + postnatal age) was used in an analysis of covariance to evaluate carnitine supplementation on these outcome measures. The analysis of covariance resulted in modest reduction in variability and had little effect on statistical power. Therefore, the outcome measures were analyzed using either a paired or unpaired Student's *t*-test.

RESULTS

The study population weighed 1.49 ± 0.67 kg (mean ± SD) and had a mean gestational age of 31.7 ± 4.5 weeks, postnatal age of 2.4 ± 1.4 weeks, and postconceptual age of 35.0 ± 4.4 weeks. There was no significant difference for any demographic variable between treatment and control groups (Table I). Neonates did not have documented or suspected sepsis while enrolled; surgical neonates were all postoperative and stable when studied; and no neonate experienced heart, kidney, or liver dysfunction. Sex distribution and diagnoses were similar within and between groups. Diagnoses included gastrointestinal surgery (n = 10), necrotizing enterocolitis (n = 15), and respiratory distress syndrome (n = 18).

Total Plasma Carnitine Concentrations

Mean plasma carnitine concentration was nearly as low at time zero (day 0) as those reported in infants receiving long-term parenteral nutrition,[9] did not change over 6 hr and was not different between groups on day 0 (mean value for all observations at prestudy presented in Table I). On study day 7, the mean carnitine concentration in the treatment group was 6–7 times higher than in the control group ($p < 0.001$) and 3.5–4 times higher than pretreatment values ($p < 0.001$) (Table I). Mean plasma carnitine concentration on study day 14 was 8–9 times higher than in the control group and 4–5 times higher than baseline values ($p < 0.001$) (Table I). Again, mean plasma carnitine concentration did not change over 6 hr on days 7 and 14; therefore, the mean for the four observations is reported in Table I. Plasma carnitine concentration for the control group did not differ significantly from day 0 through day 14, but it trended downward.

Carnitine Balance

Prestudy urinary carnitine excretion did not differ significantly between the control and treatment groups. After 2 weeks of carnitine supplementation, carnitine balance was significantly higher for the treatment group than the control group (Table I). The control group was in negative carnitine balance, which appears to be supported by declining plasma carnitine concentrations.

Weight Gain and Nitrogen Balance

Mean daily weight gain was not different between the two groups when evaluated for total time on study or in week 1. However, significantly greater weight gain was found in carnitine-supplemented neonates in week 2 (Table I). There was no obvious age-related, clinical, or nutritional cause for the significant reduction in weight gain observed in the control group during week 2. The mean nitrogen balance was significantly higher for the treatment group when compared with controls (Table I).

Fat Clearance and Utilization

Prestudy concentrations of TGY, FFA, BOB, and AA, as well as the (BOB + AA)/FAA ratio, did not vary between groups. Additionally, day 7 lipid values were not statistically different between treatment and control groups after the 2-hr fat infusion.

After 14 days of carnitine supplementation, peak TGY levels (at 2 hr or the end of the fat infusion) were significantly lower in the treatment group, as were FFA concentrations at 6 hr (Fig. 1). BOB and AA concentrations did not differ between groups (Fig. 1). The (BOB + AA)/FAA ratio was significantly higher in the treatment group on day 14 at 2 and 6 hr (Fig. 1).

DISCUSSION

This study has demonstrated increased plasma carnitine concentration and carnitine balances in neonates receiving carnitine supplementation as part of parenteral nutrition. Modest yet significant increases in nitrogen balance and weight gain (week 2) were seen in carnitine-treated neonates. A possible increase in fat utilization was also suggested on day 14 of supplementation by a decrease in FFA concentrations and an increase in the ratio of plasma ketone bodies to FFA.

Other studies have demonstrated enhanced ketogenesis with carnitine supplementation in infants and neonates receiving parenteral nutrition; however, none has shown any difference in growth parameters.[9,10] Distinct improvement in nitrogen retention was found in piglets receiving intravenous nutrition with lipid emulsion and 1.5 mg/kg L-carnitine per 24 hr when compared with isonitrogenously and isocalorically fed control animals.[18] These increases in nitrogen retention and balance in the piglet after carnitine supplementation reflected improved energy gain from exogenously administrated lipids, thus sparing protein for anabolism.

Our results show that 50 μmol/kg/day for 7 days of intravenous carnitine administration increased total plasma carnitine concentrations to those observed in

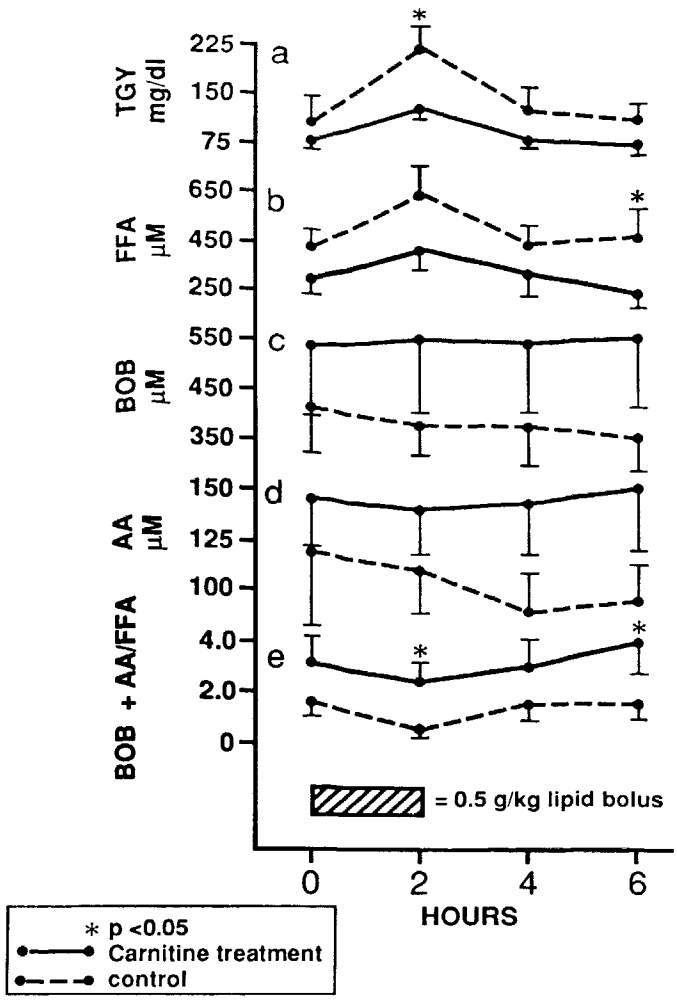

FIG. 1. Mean ± SEM for treatment and control neonates receiving a lipid infusion at time 0 through 2 hr. Treated neonates received 14 days of L-carnitine supplementation. *a*, plasma triglyceride concentrations; *b*, plasma-free fatty acid concentrations; *c*, plasma β-hydroxybutyrate concentrations; *d*, plasma acetoacetate concentrations; and *e*, the ratio of ketone body concentration/free fatty acid concentration. *Statistical significance between means of carnitine-treatment *vs* control groups for observed times.

breast-fed neonates (44.8 ± 15.7 nmol/ml, n = 29; PR Borum, personal communication) or neonates fed carnitine-containing formula.[19,20] An additional week of carnitine administration of 100 µmol/kg/day resulted in total plasma carnitine concentrations above those reference values. The intakes were greater and were given over a more prolonged period than in previous studies evaluating intravenous carnitine supplementation in neonates receiving parenteral nutrition and may explain why repletion was not accomplished in the past.[11,12]

In our study, baseline carnitine excretion in both treatment and control patients were very low compared with breast-fed or formula-fed (milk protein) neonates.[19] Carnitine supplementation was associated with positive carnitine balance. On average, 54% of exogenous carnitine was retained and was associated with normal carnitine excretion, which suggests repletion of tissue stores.[7] Tissue repletion could only be substantiated by tissue carnitine assessment, which was not accomplishable in these neonates. The control neonates were in negative carnitine balance and their plasma carnitine concentrations declined during the 2-week study period.

Insufficient supply or reduced metabolic availability of nonprotein calories can result in increased use of protein for energy production with an associated loss of nitrogen.[21] Both carbohydrate and fat can spare nitrogen losses, depending on the clinical condition.[22] Inasmuch as nitrogen and caloric intakes were similar for both groups in the present study, and enhanced ketogenesis [suggested by decreased FFA concentrations and increased (BOB + AA)/FFA ratio] was found only in the treatment subjects, increased nitrogen balance in the carnitine-supplemented neonates supports improved anabolic use of exogenous protein secondary to enhanced lipid utilization.

Weight gain was not different between treatment and control groups in week 1, although significant differences were found in week 2. This does not appear to be simply a function of less rapid growth as control neonates approach a postconceptual age of 38 to 40 weeks, where weight gain is expected to slow. At termination of the study, postconceptual age was 35.7 ± 4.3 in the treatment group *vs* 36.0 ± 4.2 in the control group. The greater weight gain in treatment neonates and decreasing weight gain in week 2 in controls was associated with increasing plasma carnitine concentrations in the treatment group while control group concentrations remained very low. We did not determine whether decreased plasma carnitine concentrations reflected depletion in tissues, but this association seems likely.[8] Decreased FFA concentrations and increased (BOB + AA)/FFA ratios were shown only in week 2 of the study; this observation may explain why weight gain differences were found only later in the study. No differences were seen in protein and caloric intakes within or between treatment and control groups for weeks 1 and 2, a finding which indicates that superior weight gain in the treatment group in week 2 was not simply the result of increased substrate delivery.

We were not able to demonstrate consistent and significant increases in ketone body production in carnitine-supplemented neonates at 7 or 14 days, although FFA consumption appears accelerated in the treatment group 4 hr after the lipid infusion was completed. We did show, as have others,[10] an increase in BOB/FFA ratios [reported as (BOB + AA)/FFA]. These ratios (or the reciprocal values) have been proposed as indicators of fatty acid oxidation.[7,21] Even with careful consideration of study design, wide intersubject/intrasubject variation seems to have prevented the demonstration of significant differences in BOB and AA concentrations, although the trends in mean concentrations of each are consistent with enhanced ketogenesis. The reason why a more profound difference in ketone body production was not demonstrated in this study population may relate to the degree of carnitine depletion secondary to the length of carnitine abstinence. For example, in a group of orally supplemented patients[4] who were, on average, over 3 months old, compared to the present study population

who were just over 2 weeks of age, the mean baseline plasma carnitine concentration was 9.4 ± 5.6 nmol/ml, compared with 14.9 ± 7.1 nmol/ml in the present study. Also, the older group of infants had higher FFA and lower BOB and AA concentrations at pretreatment. Further, the older neonates had the lowest carnitine values, and these subjects cleared and utilized fat less effectively than the younger neonates during the pretreatment period.[25] In the present study, gestational age was poorly predictive of plasma carnitine status and lipid utilization, contrary to findings by other investigators who showed positive correlation of muscle carnitine concentrations and gestational age.[26] The reason for this discrepancy is not apparent.

It is worth highlighting that these measures of fat metabolism represent the isolated effect of the 2-hr lipid bolus. The effect of continuous lipid delivery between boluses was minimized by allowing a 12- to 16-hr clearance period prior to each lipid challenge. The absence of an effect of the continuous lipid delivery can be readily appreciated by the lack of significant difference in any lipid parameter at time 0 (Fig. 1).

Novak and co-workers[27] reported lower plasma TGY and FFA concentrations, and more recently Olson et al[28] found significantly lower FFA concentrations and medium-chain dicarboxylic acids in term infants fed carnitine-supplemented soy protein formula when compared with control infants receiving unsupplemented formula. Novak et al concluded that the low plasma TGY concentrations (presumably from increased TGY metabolism) were related to an increase in the uptake of FFA for the formation of acylcarnitines. Our data support this hypothesis; that is, carnitine administered to carnitine-deficient neonates increased lipid clearance. After 2 weeks of intravenous carnitine supplementation, peak plasma TGY concentrations and terminal FFA concentrations, in response to a 2-hr fat infusion, were significantly lower in the treatment group. We did not, however, measure acylcarnitines; therefore, we cannot be sure that the lower peak TGY and FFA concentrations relate solely to increased utilization. It is clear that improved TGY clearance was not related to heparin-induced enhancement of lipoprotein lipase activity because heparin was not used during the study.[29]

In summary, intravenous carnitine supplementation in preterm neonates receiving parenteral nutrition resulted in increased plasma carnitine concentration, increased carnitine and nitrogen retention, and greater weight gain. Enhanced ketogenesis was not clearly demonstrated in carnitine-supplemented neonates but may relate more to the sensitivity of the testing instrument than to the absence of a carnitine-induced effect. Enhanced lipid clearance was associated with carnitine treatment. Further studies will need to be completed before a recommendation for routine carnitine use in parenterally fed neonates can be made.

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