0148-6071/06/3005-0421$03.00/0
JOURNAL OF PARENTERAL AND ENTERAL NUTRITION
Vol. 30, No. 5
Printed in U.S.A.

Original Communications

Relative Bioavailability of Carnitine Supplementation in Premature Neonates

Catherine M. Crill, PharmD*†‡§; Michael L. Christensen, PharmD*†‡§; Michael C. Storm, PhD*‡; and Richard A. Helms, PharmD*†‡§

*From the *Departments of Pharmacy and †Pediatrics, ‡Center for Pediatric Pharmacokinetics and Therapeutics at the University of Tennessee Health Science Center, Memphis, Tennessee; and §Methodist Le Bonheur Healthcare, Memphis, Tennessee*

ABSTRACT. *Background:* Carnitine is an important nutrient in the infant diet. We compared total plasma carnitine concentrations in premature neonates supplemented with carnitine *via* parenteral and enteral nutrition. *Methods:* This is a *post hoc* analysis of plasma total carnitine concentrations and carnitine intake in neonates randomized in a previous study to receive 20 mg/kg/d carnitine supplementation over 8 weeks. Neonates received L-carnitine initially *via* parenteral nutrition (PN). When neonates were fed enterally, oral supplementation of L-carnitine was given in divided doses with each feeding. *Results:* Sixteen neonates (27 ± 2 weeks gestation; 2.9 ± 1.0 days postnatal age at enrollment; 965.6 ± 279.1 g birth weight) are included. Concentrations were below reference range (31.1–60.5 nmol/mL) at baseline and exceeded reference range from week 1 through the last study period. Concentrations were not different from week 1 (108 ± 49) through weeks 4 (87 ± 34) and 8 (83 ± 31). Carnitine intakes and concentrations were compared in neonates receiving 100% parenteral carnitine at week 1 (n = 6) and 100% enteral carnitine at week 8 (n = 8). Concentrations at week 1 (100.1 ± 27.9) were not different (p = .19) from week 8 (78.6 ± 29.3); an estimate of relative bioavailability was 78.6%. Bioavailability with paired analysis of neonates (n = 5) receiving 100% parenteral carnitine at week 1 and 100% enteral carnitine at week 8 was 83.7% ± 41.2% (30.1%–140.6%). *Conclusions:* Parenteral and enteral supplementation of 20 mg/kg/d carnitine results in plasma total carnitine concentrations that exceed the reference range. Concentrations are not different between parenteral to enteral supplementation, suggesting that enteral carnitine is well absorbed when given daily in divided doses with enteral feedings. (*Journal of Parenteral and Enteral Nutrition* **30**:421–425, 2006)

Carnitine is synthesized from methionine and lysine in the liver and kidney and is important for the transport of long-chain fatty acids across the mitochondrial membrane, where they can undergo β-oxidation to produce energy. Carnitine may be considered a conditionally essential nutrient in the neonatal population due to a reduced ability of the neonate to synthesize carnitine. Premature neonates may be particularly vulnerable to carnitine deficiency due to a lack of placental transfer in the third trimester and decreased tissue stores.[1–4] Exogenous intake of carnitine in this population is important to prevent deficiency.

The benefits of carnitine supplementation in parenteral and enteral feedings on neonatal nutrition markers, primarily enhanced fatty acid oxidation and clearance, improved lipid tolerance, and increased nitrogen balance, are well documented.[5–10] In addition, carnitine supplementation has been found to be important for weight gain in the neonatal population.[9,10]

Carnitine oral bioavailability has been reported to be as low as 5%–18%.[11–14] This number may be in part due to a dose dumping effect after single-oral-dose pharmacokinetic studies. Due to concerns over reduced bioavailability, larger doses of enteral carnitine are often used. Our group found in an earlier study that continuous gastric tube supplementation of 10 mg/kg/d L-carnitine over 7 days in infants receiving prolonged parenteral nutrition (PN) produced total plasma carnitine concentrations that were 3.5–5 times higher than those of nonsupplemented infants and were within the lower end of the range of concentrations of human-milk- or formula-fed infants.[7,15–17] The purpose of the current study was to compare the parenteral and enteral supplementation of carnitine on total plasma carnitine concentrations in premature neonates who initially required PN and were transitioned to enteral nutrition (EN) during an 8-week study period.

MATERIALS AND METHODS

This is a *post hoc* analysis of a prospective, randomized, placebo-controlled, double-blinded trial evaluating the effect of carnitine supplementation in premature neonates. Neonates were enrolled in the study from 2 Level 3 neonatal intensive care units (NICU) in Memphis, Tennessee. The institutional review boards of the University of Tennessee Health Science Center and Methodist Le Bonheur Healthcare approved the study. Informed parental consent was obtained prior to enrollment. Neonates were eligible for enrollment if they were ≤4 days of age, ≤32 weeks gestation, had a

Received for publication January 11, 2006.
Accepted for publication April 28, 2006.
Correspondence: Catherine M. Crill, PharmD, BCPS, BCNSP, 26 South Dunlap, Suite 210, Memphis, TN 38163. Electronic mail may be sent to ccrill@utmem.edu.

birth weight of ≤1500 g, and initially required PN support. Neonates were excluded from the study if they had inborn errors of metabolism, chromosomal abnormality, end-stage liver or renal disease, were receiving peritoneal dialysis or hemofiltration, or had grade IV intraventricular hemorrhage (IVH). Only the neonates randomized to receive carnitine supplementation were included in this *post hoc* analysis.

Carnitine supplementation was given *via* both PN and EN during the study period. When neonates were receiving PN, 130 mg/L of IV L-carnitine (Carnitor; Sigma Tau Pharmaceuticals, Gaithersburg, MD) was added to the solution so that an infusion rate of 150 mL/kg would provide approximately 20 mg/kg/d. The addition of L-carnitine to the PN solutions was done at the time of PN preparation in the pharmacy at each of the hospitals.

Once the neonates began the transition to enteral feedings, oral syringes containing 1 mL (10 mg/mL) oral L-carnitine (Carnitor) were compounded under clean conditions in the pharmacy at LeBonheur Children's Medical Center and transported to the NICUs under refrigerated conditions. NICU nursing staff added the contents of 1 syringe to each 90-mL feeding (equivalent to 110 mg/L of carnitine) of either Pregestimil, Nutramigen, or Enfamil Premature (Mead Johnson Nutritionals, Evansville, IN) or expressed human milk such that an enteral feeding rate of 150–180 mL/kg/d would provide approximately 17–20 mg/kg/d of carnitine. Total carnitine intake (mg/kg/d) was calculated according to reported content in enteral diet in addition to the amount supplemented in parenteral and enteral formulas. The commercial products contained a reported 13.5 mg/L of carnitine (per product labeling), and the carnitine content of expressed human milk was estimated at 10.5 mg/L.[18]

Blood for plasma total carnitine concentrations was drawn at baseline and weeks 1, 2, 4, 6, and 8. Samples were centrifuged under refrigeration within 1 hour of collection, and the plasma was stored at −70°C until analysis. Carnitine concentrations were analyzed in duplicate *via* a radioenzymatic assay.[19] The reference plasma total carnitine concentration was 31.1–60.5 nmol/mL.[16,17,20] All laboratory analysis was conducted in the Center for Pediatric Pharmacokinetics and Therapeutics laboratory at the University of Tennessee Health Science Center, Memphis, TN.

Relative bioavailability was calculated by dividing the average total carnitine concentration at week 8 for all neonates receiving 100% enteral carnitine by the average total carnitine concentration at week 1 for all neonates receiving 100% parenteral carnitine and then multiplying the result by 100. Bioavailability was calculated for neonates who had paired samples (100% parenteral carnitine at week 1 and 100% enteral carnitine at week 8).

Statistical analysis of data was conducted with repeated-measures ANOVA to determine differences across the study periods. Student's *t*-test was used when analyzing grouped samples and paired *t*-test for paired samples. Data are reported as mean ± SD. Data with p values $< .05$ are considered significantly different.

TABLE I
Characteristics of the 16 study patients

Characteristic	n = 16
Male*	4
Ethnicity*	
African-American*	4
White*	12
Cesarean section*	7
Gestation (wk)†	27 ± 2.0 (24–30)
<25*	2
25–29*	11
≥30*	3
Birth weight (g)†	965.9 ± 279.1 (449–1476)
≤750*	4
751–1000*	6
>1000*	6
Postnatal age at enrollment (d)†	2.9 ± 1.0 (1–4)
Discharge before 4 wk*	2
Discharge between 4 and 8 wk*	5

*Data are number of patients. †Data are mean ± SD (range).

RESULTS

Seventeen neonates were randomized in the prospective trial to receive carnitine supplementation. One neonate died within 14 days of study enrollment and was not included in the data analysis (per protocol). Therefore, 16 neonates are included in this *post hoc* assessment of carnitine bioavailability. Patient characteristics are reported in Table I.

Plasma total carnitine concentrations are represented in Figure 1. Carnitine concentrations were below reference range at baseline (23.8 ± 13.6) and were significantly increased from baseline to all other study points (107.9 ± 49.2, week 1; 99.7 ± 28.2, week 2; 86.6 ± 33.7, week 4; 86.4 ± 24.9, week 6; 83.1 ± 30.6, week 8). Concentrations exceeded the reference range and were not different from week 1 through the last study period. Percent of total calories from the enteral route increased across the study and was >50% during study weeks 2 and 4 and >80% by study weeks 6 and 8. Statistically significant differences ($p < .05$) in percent of total calories from the enteral route exist between baseline (10 ± 16) and weeks 4 (72 ± 39) and 8 (84 ± 36) and between week 1 (35 ± 36) and week 8 (84 ± 36).

Table II presents carnitine intakes and plasma total carnitine concentrations for those neonates who were receiving 100% parenteral carnitine supplementation at week 1 (n = 6) and 100% enteral carnitine supplementation at week 8 (n = 8). Although concentrations decreased when neonates transitioned from parenteral to enteral supplementation, they were not significantly different ($p = .19$) and were maintained well above the reference range. There was also no difference in carnitine concentration ($p = .25$) when analyzing paired data for 5 of these neonates who were receiving 100% parenteral carnitine at week 1 and 100% enteral carnitine at week 8. Estimates of relative bioavailability in the grouped and paired neonates were approximately 80%.

DISCUSSION

In this *post hoc* analysis, we found that 20 mg/kg/d carnitine supplementation resulted in plasma total

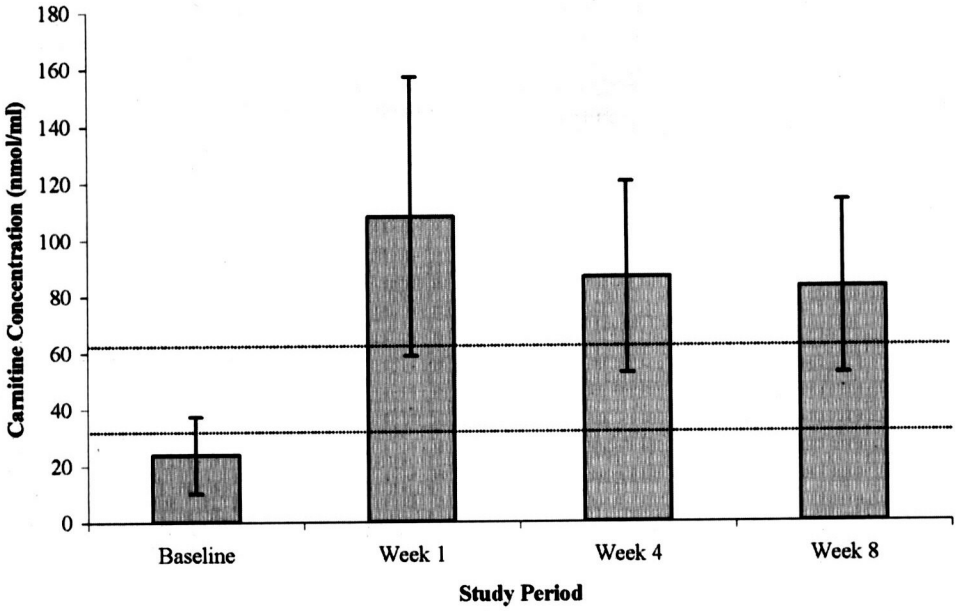

FIGURE 1. Plasma total carnitine concentrations by study period. Number of patients at each assessment is as follows: baseline (16), week 1 (15), week 4 (14), and week 8 (9). Data are represented as mean ± SD. The 2 horizontal lines delineate the reference plasma total carnitine concentrations (31.1–60.5 nmol/mL).[16,17,20] Statistically significant differences ($p < .05$) in carnitine concentration exist between baseline and all other study periods (weeks 1, 4, and 8).

carnitine concentrations that exceeded the reference range regardless of whether the neonates were receiving carnitine *via* the parenteral or enteral route. In addition, our data suggest that the enteral carnitine supplementation regimen used in this study produced an estimated relative bioavailability of approximately 80%, well above that reported previously in the literature.

Carnitine bioavailability after oral dosing has previously been reported to range from 5% to 18%.[11–14] Most of these studies have evaluated bioavailability after large single oral doses of carnitine (2–6 g or 100 mg/kg).[11–13] One of the studies evaluated bioavailability after multiple doses (steady state assumed by day 3) of 2 g carnitine every 12 hours.[14] In contrast to these studies, Rebouche and Chenard[21] documented a bioavailability of 54%–87% after administering a radiolabeled dose of L-carnitine to people receiving a normal diet that was either high or low in carnitine content. Of interest, the bioavailability was dependent on the amount of carnitine in the diet. Similarly, investigators studying the effects of orally administered carnitine in rats found the fraction absorbed to be 33%–42% compared with 96%–100% when giving a high compared with a low carnitine dose (100 *vs* 0.05 μmol/rat).[22,23] Bioavailability seems to decrease when using larger doses. Harper et al[11] found that the bioavailability of a 2-g dose was 16% compared with only 5% with a 6-g dose.

The lower estimates of bioavailability may in part be due to a dose-dumping effect after administering single oral doses. In this study, we gave 20 mg/kg/d, and we gave a portion of the total daily oral L-carnitine dose with each feeding, essentially mimicking continuous enteral infusion. The fact that carnitine concentrations were maintained when neonates made the transition

TABLE II
Carnitine bioavailability

	Intake (mg/kg/d)		Plasma total carnitine concentration (nmol/mL)
Grouped			
Wk 1 (n = 6)	16.9 ± 5.6 (10.8–24.5)		100.1 ± 27.9 (58.5–125.1)
Wk 8 (n = 8)	17.9 ± 4.3 (8.4–23.1)		78.6 ± 29.3 (29.7–105.2)
p Value	.71		.19
Relative bioavailability (%)*		78.6	
Paired			
Wk 1 (n = 5)	18.1 ± 5.2 (11.9–24.5)		105.4 ± 27.7 (58.5–125.1)
Wk 8 (n = 5)	16.9 ± 5.4 (8.4–23.1)		79.9 ± 25.3 (37.6–105.2)
p Value	.78		.25
Bioavailability (%)†		83.7 ± 41.2 (30.1–140.6)	

Data are mean ± SD (range). Carnitine intake represents supplemented amount in addition to that reported in formula/human milk.
*Relative bioavailability was calculated in grouped neonates (all neonates receiving 100% parenteral carnitine at wk 1 and 100% enteral carnitine at wk 8) as follows: (steady-state concentration *via* enteral dosing/steady-state concentration *via* parenteral dosing) × 100.
†Bioavailability was calculated in neonates who had paired samples at wk 1 and 8 as follows: (steady-state concentration *via* oral dosing/steady-state concentration *via* parenteral dosing) × 100.

from parenteral to enteral carnitine supplementation suggests that this oral dosing regimen avoids potential dose-dumping effects. In addition, because our carnitine concentrations exceeded the reference range from weeks 1 through 8, our data may support the use of smaller doses in the future.

Two recent reviews delineated issues surrounding L-carnitine absorption and the pharmacokinetics of exogenous L-carnitine.[24,25] The majority of absorption of exogenous carnitine occurs by passive diffusion in the small intestine. For this reason, certain patient populations, such as those with intestinal resections or other functional abnormalities of the gastrointestinal tract, may not be capable of optimal exogenous carnitine absorption. A case report has documented carnitine deficiency in a 3-year-old patient with short bowel syndrome who was receiving oral carnitine supplementation during chronic PN therapy.[26] Because carnitine is excreted almost completely *via* the kidneys, patients with renal dysfunction may not be able to adequately eliminate carnitine.[24,25]

Two other studies evaluating enteral carnitine supplementation have reported carnitine concentrations exceeding the reference range used in this study.[27,28] One study, published by Shortland et al,[28] had a similar study design to the current study in that the authors reported plasma total carnitine concentrations out to 28 days in premature neonates receiving 25 mg/kg/d carnitine supplementation (initially given IV until enteral feedings were tolerated).[28] Mean concentrations ranged from 160 nmol/mL on day 7 to 104 nmol/mL on day 28. This paper did not report when the neonates were receiving parenteral compared with enteral carnitine supplementation; however, the concentrations are similar to what we found in the current study.

The other study, published by Melegh et al,[27] reported plasma total carnitine concentrations of 81–99 nmol/mL after only 7 days of receiving 9.6 mg/kg/d divided equally among feedings. The carnitine concentrations in this study were very different from the earlier data that our group had published in the same year.[7] In both the Melegh et al[27] and Helms et al[7] studies, subjects received approximately 10 mg/kg/d oral carnitine; however, the plasma total carnitine concentrations in the Helms et al[7] study after 7 days were approximately one-half to one-third those reported by Melegh et al.[27] These differences may be explained by characteristics of the study populations and their underlying carnitine status. Whereas the Melegh et al[27] study enrolled preterm neonates between 1 and 2 weeks of age who had been receiving a combined enteral and parenteral diet, the Helms et al[7] study enrolled infants (mean age, 99 ± 71 days) who had been receiving long-term PN without carnitine supplementation. It is not surprising, then, that the baseline carnitine status of the infants in the Helms et al[7] study (9.4 ± 6.7 nmol/mL) suggested carnitine deficiency, whereas the baseline carnitine status of the neonates in the Melegh et al[27] study exhibited reference range concentrations (36.7 ± 5.2 nmol/mL in control compared with 33.8 ± 2.5 nmol/mL in supplemented neonates).[7,27] In addition, all of the infants enrolled in the Helms et al[7] study were gastrointestinal surgery patients with underlying disease of the bowel (eg, necrotizing enterocolitis and gastroschisis) and many had significant bowel loss. The fact that these infants were able to achieve plasma carnitine concentrations within the 30–40 nmol/mL range with 10 mg/kg/d oral carnitine supplementation over 7 days is actually quite remarkable, given their underlying gastrointestinal disease, and further supports a much greater bioavailability than previously thought.[7]

Although not statistically significant and still exceeding reference range, carnitine concentrations in the current study decreased when neonates transitioned from parenteral to enteral supplementation. Although this decrease may represent reduced bioavailability with enteral supplementation, it could also be the result of maturity of renal function, and thereby increased renal carnitine elimination, in this group of premature neonates. If, in fact, the decrease was due to renal maturity, this may imply an even greater bioavailability than what we have reported in this paper.

Our most recent data, along with the work of Shortland et al[28] and Melegh et al,[27] suggest that a shorter duration of carnitine abstinence or the use of an initial period of parenteral carnitine supplementation promotes the achievement and maintenance of carnitine concentrations that are above the reference range. In other studies of enteral carnitine supplementation, in which enrolled subjects were either already carnitine deficient or were initially supplemented *via* the enteral route, carnitine concentrations have only reached reference range, despite an increased length of supplementation (up to 5 months) and increased doses.[7,8,29–33] Our data suggest that when using a similar dosing regimen, reduced carnitine doses are likely to produce steady-state concentrations that are within reference range in a shorter window of time (7–14 days).

CONCLUSION

Parenteral and enteral supplementation of 20 mg/kg/d carnitine results in plasma total carnitine concentrations that exceed the reference range. In addition, concentrations are not different when neonates transition from supplementation *via* parenteral to enteral route, suggesting that enteral carnitine is well absorbed when given in small doses across a 24-hour period.

ACKNOWLEDGMENTS

Supported in part by the Le Bonheur Children's Medical Center Small Grants Program and Sigma Tau Pharmaceuticals.

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