L-Carnitine: effect of intravenous administration on fuel homeostasis in normal subjects and home-parenteral-nutrition patients with low plasma carnitine concentrations[1-4]

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ABSTRACT We studied the effects of intravenous L-carnitine on the metabolism of fatty acids, ketone bodies, glucose, and branched-chain amino acids in four normal volunteers and four patients on long-term home parenteral nutrition (HPN) with low plasma carnitine concentrations. Substrate kinetics were determined by use of [1-^{14}C]palmitate, [3,4-$^{13}C_2$]-acetoacetate, [6,6-$^{2}H_2$]glucose, and [5,5,5-$^{2}H_3$]leucine before and during a 3-h intravenous infusion of L-carnitine. HPN patients were restudied after 1 mo of nightly intravenous carnitine administration. HPN patients tolerated the short-term fast well, exhibiting neither hypoglycemia nor hypoketonemia. Intravenous carnitine had no effect on rates of fatty acid oxidation, ketone body production, glucose production, or leucine kinetics in either group. Routine addition of carnitine to the HPN regimen does not appear to be necessary. The failure of L-carnitine administration to have discernable effects on intermediary metabolism in normal volunteers casts doubt on its role in the treatment of a variety of medical conditions. *Am J Clin Nutr* 1989;49:618–23.

KEY WORDS Carnitine, parenteral nutrition, glucose, free fatty acids, ketone bodies, leucine, kinetics, oxidation

Introduction

L-Carnitine (β-hydroxyl-γ-trimethylamino-butyric acid) was initially characterized and synthesized by Tomita and Sendju in 1927 (1). In recent years L-carnitine has been marketed in health food stores as a nutritional supplement (eg, L-carnitine, 250 mg capsules, Solgar Company, Inc, Lynbrook, NY). In literature published for the general public, it has been touted as useful in the management of myocardial infarction (2), diabetes (3), and obesity (4). The major biochemical function of L-carnitine is in the mitochondrial transport of long-chain fatty acids (5); if L-carnitine has therapeutic efficacy in heart disease, diabetes, obesity, and other medical conditions, it likely would exert its effects via this mechanism (6). Although a correlation between hepatic carnitine content and ketogenic capacity was observed in most (7) but not all (8) experimental circumstances, it has not been established whether carnitine availability is rate limiting for long-chain fatty acid oxidation in humans. In addition, studies in rat liver indicate that carnitine may play a role in branched-chain amino acid metabolism (9).

It was recently demonstrated (10) that patients on long-term home parenteral nutrition (HPN) may have low plasma carnitine concentrations; whether this phenomenon is accompanied by defects in fatty acid or branched-chain amino acid metabolism is unknown. The present studies were therefore undertaken to determine whether carnitine administration results in augmented fatty acid oxidation in normal man and whether low plasma carnitine concentrations in HPN patients are associated with impaired fatty acid oxidation, correctable by administration of intravenous carnitine.

Materials and methods

Ethyl[3,4-$^{13}C_2$]acetoacetate, ethyl[1,2,3,4-$^{13}C_4$]acetoacetate, [6,6-$^{2}H_2$]glucose, and [5,5,5-$^{2}H_3$]leucine (all > 99% moles per-

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cent enriched) were obtained from Merck, Sharpe, and Dohm Isotope Division (Pointe Claire/Duvall, Quebec, Canada). Sodium[3,4-$^{13}C_2$]acetoacetate was prepared from its ethyl ester as previously described (11) and stored at −80 °C before use. [1-^{14}C]Palmitic acid (1458 MBq/mmol in hexane) was obtained from Research Products International Corporation (Mount Prospect, IL), taken to dryness under nitrogen, resuspended in 25% human serum albumin, and sonicated in a 60 °C water bath for 10 min. The albumin solution was then diluted with 5 mmol Na_2PO_4/L buffer, pH 7.8, to a final albumin concentration of 1%, containing 2.7–5.4 MBq/mL. All four tracers were passed through 0.2 μm filters (Gelman Instrument Co, Ann Arbor, MI) and determined to be sterile and pyrogen free before use. Lithium[1,2,3,4-$^{13}C_4$]acetoacetate was prepared from its ethyl ester (11) for use as an internal standard; an aliquot of this material was converted to Li[1,2,3,4-$^{13}C_4$]D-βOHB for the same purpose (12). L-Carnitine hydrochloride (pH 4.6, 2.5% solution) was supplied by Kendall-McGaw (Irvine, CA).

Protocol

After approval by the Mayo Institutional Review Board was received, informed written consent was obtained from four HPN patients (mean duration of therapy, 4.5 y) who had previously been found to have decreased plasma carnitine concentrations. A stable clinical course, including a stable weight for at least 3 mo, was required for participation. Four age- and sex-matched volunteers were recruited to participate as control subjects.

HPN patients and control subjects were hospitalized in the Mayo General Clinical Research Center. The admission evaluation included a history, a physical examination, and laboratory studies (complete blood count, blood chemistry studies, and urinalysis). The control subjects underwent a 36-h fast before the study; HPN subjects were studied 24–48 h after cessation of intravenous nutrient infusion. All subjects were allowed free access to water during the study. On the morning of study, a 19-gauge butterfly needle was placed in a dorsal hand vein in a retrograde fashion, and the hand was maintained in a warming box (55 °C) for subsequent sampling of arterialized venous blood (13). The needle was kept patent with a slow (10–15 mL/h) controlled infusion of 0.9% NaCl. A blood sample was drawn before the infusions to serve as a blank for the gas chromatography-mass spectrometry (GC-MS) analyses. An 18-gauge catheter for infusion was placed in a forearm vein of the contralateral arm; this was also kept patent with a controlled infusion of saline. After these catheters were in place and primed, continuous infusions of Na[3,4-$^{13}C_2$]acetoacetate (~6 μmol/kg, ~0.3 $\mu mol \cdot kg^{-1} \cdot min^{-1}$), [1-^{14}C]palmitate (~1620 KBq, 8.1 KBq/min), [6,6-$^2H_2$]glucose (~20 μmol/kg, ~0.2 $\mu mol \cdot kg^{-1} \cdot min^{-1}$), and [5,5,5-$^2H_3$]leucine (~1 μmol/kg, ~0.05 $\mu mol \cdot kg^{-1} \cdot min^{-1}$) were begun simultaneously. An ice bag was kept on the [^{13}C]acetoacetate syringe during the infusion to prevent decarboxylation (11). The isotopes were infused for 2 h before blood sampling to allow isotopic equilibration.

L-Carnitine hydrochloride was infused (66 $\mu g \cdot kg^{-1} \cdot min^{-1}$ × 20 min and 33 $\mu g \cdot kg^{-1} \cdot min^{-1}$ thereafter) beginning at minute 0 and continuing to the end of the study (+180 min). Blood samples were drawn at −45, −30, −15, 0, 15, 30, 45, 60, 90, 120, 150, and 180 min of the study for determination of leucine, α-ketoisocaproate (KIC), glucose, and ketone-body isotopic enrichment and concentration as well as plasma palmitate concentration and specific activity and insulin, glucagon, and carnitine concentrations.

Breath collections were obtained at −45, −15, 60, 120, and 180 min of the study for determination of $^{14}CO_2$ excretion rate as previously described (14). At the end of the experiment, the HPN patients resumed their respective HPN formulas, infused through a central venous catheter during an 8–12-h overnight period, to which 1 g L-carnitine hydrochloride was added daily. After 1 mo of treatment with L-carnitine, the HPN patients were restudied using an protocol identical except that the acute carnitine infusion was omitted and blood sampling was limited to the base-line period (−45 through 0 min).

Analyses

Plasma leucine concentration and enrichment were determined by GC-MS (15). Plasma KIC concentration and enrichment were also determined by GC-MS with a *tert*-butyl dimethylsilation procedure (16). Ketone body isotopic enrichment was measured by a previously published technique (11); in the same analysis ketone body concentrations (acetoacetate + β-hydroxybutyrate) were determined with Li[1,2,3,4-$^{13}C_4$]-acetoacetate and Li[1,2,3,4-$^{14}C_4$]D-β-hydroxybutyrate as internal standards. Plasma glucose concentrations were determined on a YSI glucose analyzer (Yellow Springs Instruments, Yellow Springs, OH). Plasma palmitate concentration and specific activity (SA) were determined by high-performance liquid chromatography (17). Insulin (18) and glucagon (19) were determined by radioimmunoassay. Total and acyl carnitine was determined by a sensitive radioenzymatic method (20).

Calculations

Steady-state conditions were achieved with respect to plasma concentrations and specific activities of all measured values between −45 and 0 and between +90 and +180 min; therefore, values were averaged for both intervals for each subject. Rates of appearance (R_a) of glucose and ketone bodies were determined by the equation

$$R_a = \frac{(E_i - 1)F}{E_p} \quad (1)$$

where F is the isotope infusion rate and E_i and E_p are the isotopic enrichment of the tracer in the infusate and plasma, respectively. A similar calculation was made for leucine except that the $^2H_3$ enrichment in KIC, the transaminated product of leucine and a presumed indicator of intracellular leucine enrichment, was used (21). Palmitate R_a was calculated by similar steady-state calculations (17). Palmitate oxidation rate was calculated by the formula (22)

$$\text{Oxidation} = \frac{^{14}CO_2 \text{ excretion rate}}{^{14}\text{C palmitate SA (plasma)} \cdot 0.8} \quad (2)$$

Basal turnover rates and oxidation rates were compared for the precarnitine treatment study and the study after 1 mo of carnitine therapy by a paired *t* test; the effects of acute carnitine infusion were analyzed in a similar fashion. Comparisons between HPN patients and control subjects were made using a nonpaired *t* test.

Results

Total plasma carnitine concentrations were lower in HPN subjects than in control subjects during the base-line period and increased significantly during L-carnitine

TABLE 1
Plasma total carnitine and acyl carnitines*

	Normal subjects			HPN patients			
	Base line	90 min	180 min	Base line	90 min	180 min	1 mo
Total carnitine (μmol/L)	41 ± 4	105 ± 8†	120 ± 11†	28 ± 3‡	92 ± 6†	108 ± 5†	36 ± 4†
Acyl carnitines (μmol/L)	16 ± 1	26 ± 2†	29 ± 4†	9 ± 3	19 ± 7†	21 ± 7†	10 ± 3

* $\bar{x} \pm$ SEM.
† $p < 0.05$ compared with base line, same group.
‡ $p < 0.05$ compared with normal subjects.

infusion in both groups (**Table 1**). Plasma acyl carnitines also increased significantly during L-carnitine infusion. After 1 mo of daily carnitine infusion in HPN patients, base-line plasma carnitine had increased.

Palmitate concentration, R_a, and oxidation rates for both groups are depicted in **Figure 1.** Basal palmitate turnover ($p < 0.01$) and palmitate concentration ($p < 0.05$) were lower in HPN patients when compared with control subjects whereas the difference in oxidation rate did not achieve statistical significance. There was no change in these values in either group after acute carnitine infusion or in HPN patients after 1 mo of daily intravenous carnitine administration.

Figure 2 depicts total ketone body (acetoacetate + β-hydroxybutyrate) concentration and R_a for both groups. Basal ketone body concentration and turnover were slightly but not significantly lower in HPN patients compared with control subjects. No significant changes in ketone body concentration or R_a were observed in either group after acute carnitine infusion. However, ketone body R_a decreased significantly after chronic carnitine therapy in HPN patients whereas the decrease in ketone body concentration did not achieve statistical significance when compared with pretreatment values.

Leucine concentrations were slightly but not significantly lower in HPN patients than in control subjects whereas KIC concentrations were similar (**Table 2**). Leucine turnover was nearly identical in the two groups. No significant change was observed in KIC concentration or in the concentration or turnover of leucine during acute carnitine infusion in the two groups nor was change observed after 1 mo of daily carnitine infusion in HPN patients.

No difference in glucose concentration and turnover was observed between control subjects and HPN patients and no change occurred with acute or chronic carnitine administration (Table 2).

Plasma glucagon concentrations were lower in HPN patients than in normal control subjects although the difference did not achieve statistical significance (Table 2). Insulin concentrations were similar in the two groups; no changes in glucagon or insulin concentrations were observed in response to carnitine administration in either group.

Discussion

The present studies were undertaken to determine whether carnitine administration influences rates of fatty acid oxidation, ketogenesis, and leucine kinetics in normal subjects and HPN patients and whether a defect in fatty acid oxidation is present in HPN patients. The failure of intravenous infusion of carnitine to further augment rates of fatty acid oxidation in either group suggests that L-carnitine availability is not rate limiting for this process at least under conditions of short-term fasting. Although it is possible that a brief (3-h) infusion might not affect intracellular carnitine concentrations, the observed significant increase in plasma acyl carnitines suggests that the administered L-carnitine was indeed transported into tissues in significant quantities. Moreover, we have documented that 1 mo of intravenous carnitine therapy restores hepatic carnitine stores in HPN patients to normal (23).

McGarry et al (7) showed a direct correlation between hepatic concentration of carnitine and ketogenic capacity as well as stimulation of ketogenesis from oleate when perfused rat liver was exposed to carnitine. Carnitine also augmented ketogenesis in a more recent study (24) in which it was added to a hepatocyte preparation but it became antiketogenic at concentrations of 40 mmol/L and also was associated with lower plasma ketone body concentrations when administered orally to rats at doses of 200 mg/100 g body wt. Although the physiologic relevance of such concentrations and doses is not clear, a dissociation between carnitine availability and hepatic ketogenic capacity was demonstrated (8). The results of the present study appear to be at variance with a report by Avogaro et al (25) in which L-carnitine was infused into normal subjects and an increase in plasma ketone body concentrations and a decrease in plasma free fatty acid concentrations were observed. The higher dose of carnitine used in that study, however, together with infusion of vitamin C in the control experiments and lack of information about the dietary status of the subjects studied make interpretation and comparison difficult. More recently (26) no significant differences in plasma ketone body or free fatty acid concentrations were observed in neonates receiving a predominantly lipid-based

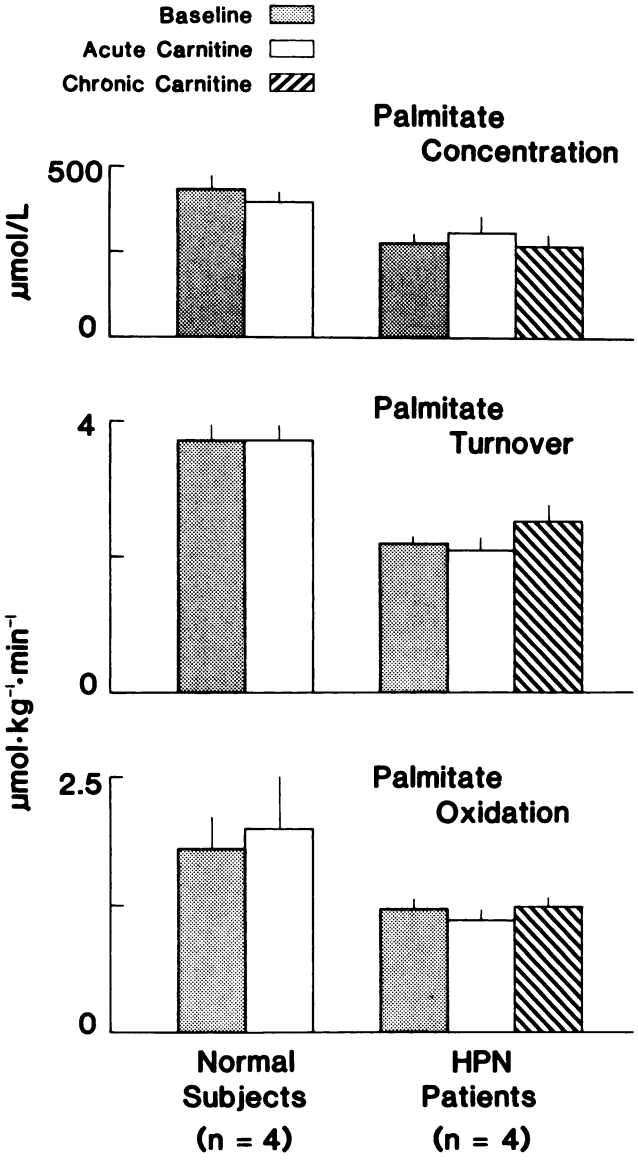

FIG 1. Plasma palmitate concentration (upper panel), turnover (middle panel), and oxidation (lower panel) in normal subjects and home-parenteral-nutrition patients before and after intravenous carnitine administration.

total parenteral nutrition (TPN) supplemented with oral carnitine when compared with control neonates, a finding consistent with the results of the present study.

The present study also demonstrates that HPN patients with low plasma carnitine concentrations tolerate a short-term fast well, exhibiting neither the hypoglycemia (27) nor hypoketonemia (27, 28) that would be anticipated with profound depletion of body stores of carnitine. Reactive hypoglycemia in a patient on long-term TPN improved with administration of intravenous carnitine in a single report (29). In that study, however, hypoglycemia was not documented (lowest plasma glucose value, 3.8 mmol/L) and no defect in fatty acid oxidation was demonstrated. It is possible that sufficient depletion of body stores of carnitine could occur in gut-failure patients on HPN so that a true functional carnitine deficiency would result although there is no evidence for this from our study. In our study palmitate oxidation was lower in HPN patients than in control subjects although the difference was not significant. It is possible that our study failed to detect small differences in the measured variables because of the small number of subjects studied. The lower palmitate R_a and concentration in HPN patients likely reflects an earlier stage in the evolution of fasting compared with control subjects; the relationship between cessation of infusion of large quantities of intravenous nutrients and the expected increase in palmitate oxidation and ketone body production may be temporally different from that in a fast in which the beginning is marked by completion of a meal. The explanation for lower ketone body production observed in HPN patients after 1 mo of carnitine therapy is not clear; this finding

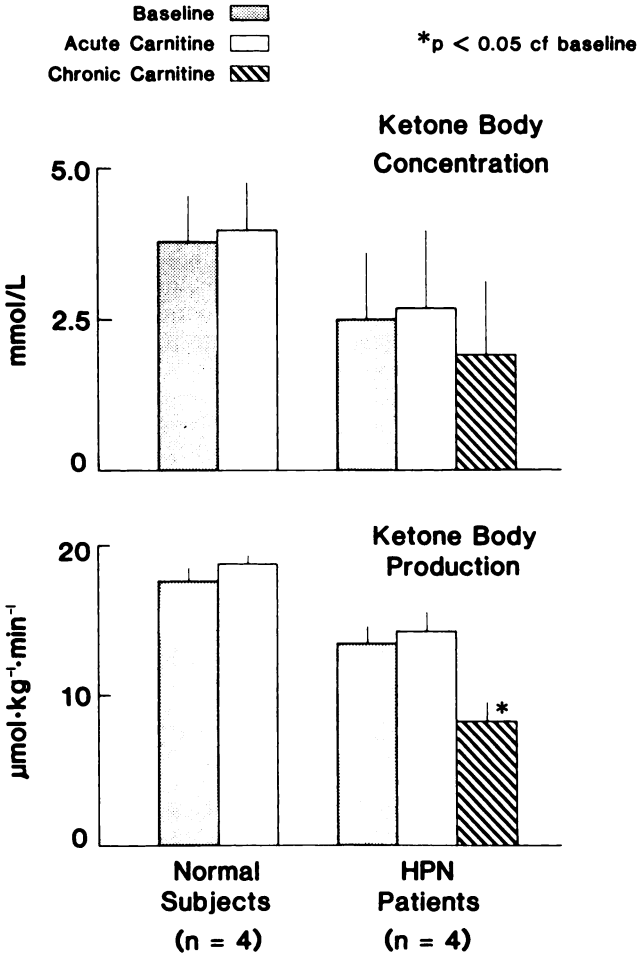

FIG 2. Plasma ketone body concentration (upper panel) and production (lower panel) in normal subjects and home-parenteral-nutrition patients before and after intravenous carnitine administration.

TABLE 2
Effect of carnitine infusion on plasma concentration of leucine, KIC, glucose, insulin, and glucagon and leucine and glucose turnover*

	Normal subjects		HPN patients		
	Base line	90–180 min	Base line	90–180 min	1 mo
Leucine concentration (μmol/L)	136 ± 20	138 ± 20	93 ± 17	97 ± 18	87 ± 16
Leucine turnover (μmol·kg^{-1}·min^{-1})	2.1 ± 0.1	1.8 ± 0.2	2.1 ± 0.2	1.9 ± 0.2	2.1 ± 0.2
KIC concentration (μmol/L)	58 ± 8	64 ± 10	65 ± 12	62 ± 12	59 ± 11
Glucose concentration (mmol/L)	3.1 ± 0.2	2.9 ± 0.2	2.9 ± 0.2	2.7 ± 0.2	3.3 ± 0.3
Glucose turnover (μmol·kg^{-1}·min^{-1})	9.4 ± 1.2	9.1 ± 0.4	9.9 ± 0.7	8.9 ± 0.7	10.1 ± 0.8
Insulin (pmol/L)	37 ± 7	38 ± 6	36 ± 2	34 ± 2	40 ± 3
Glucagon (pmol/L)	93.2 ± 13	86.4 ± 3.4	68.9 ± 21	67.4 ± 19	68.3 ± 19

* $\bar{x}$ ± SEM.

may be related to the relatively small number of subjects studied. It seems less likely that it is a reflection of an actual antiketogenic effect of carnitine.

It was suggested (9) that carnitine may enhance mitochondrial transport of branched-chain α-ketoacids and therefore could be a key regulator of branched-chain amino acid oxidation. In the present study neither acute administration of intravenous carnitine nor 1 mo of carnitine supplementation in HPN patients altered plasma leucine kinetics or plasma concentrations of leucine or KIC. Although determination of leucine oxidation was not possible because of concurrent use of ^{14}C palmitate and ^{13}C acetoacetate, it seems unlikely that a significant effect on branched-chain amino acid oxidation could occur in the absence of changes both in leucine kinetics and in plasma concentrations of leucine and KIC. The apparent contradiction between the in vitro findings of Paul and Adibi (9) and our results could potentially be explained by a permissive rather than an active role for carnitine in branched-chain ketoacid transport.

Our data are also inconsistent with the results of Böhles et al (30) who showed that N balance is enhanced when carnitine is added to a TPN regimen in piglets. In addition to the possibility of species differences, carnitine improved N balance that was already positive on a hypercaloric feeding regimen. Our results also fail to document an antilipolytic effect of carnitine suggested by Böhles et al because we observed no change in palmitate R_a and concentration after carnitine administration.

In summary, acute administration of carnitine to normal subjects and HPN patients has no apparent effect on rates of palmitate, ketone body, glucose, or leucine metabolism. Although L-carnitine has been promoted in the popular literature for use in such disparate conditions as myocardial infarction, diabetes, and obesity, scientific data to support such therapy is not available. Moreover, it seems unlikely that L-carnitine would have favorable effects in these conditions because, from the present data, L-carnitine has no pharmacologic effects on fatty acid or branched-chain amino acid metabolism. HPN patients with low plasma carnitine concentrations tolerate a short-term fast well, exhibiting none of the abnormalities that would be expected if a functional carnitine deficiency were present. Routine addition of carnitine to the HPN regimen, therefore, does not appear to be necessary.

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