Increased plasma carnitine in trauma patients given lipid-supplemented total parenteral nutrition[1-2]

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ABSTRACT The purpose of this study was to determine the effects of altering the fuel substrate mix of total parenteral nutrition (TPN) on plasma and urinary carnitine in trauma patients. TPN solutions were either 100% carbohydrate (CHO) based or lipid based (70% CHO, 30% lipid). There were statistically significant ($p < 0.05$) increases in plasma levels of free carnitine, short-chain acyl carnitine, and total carnitine in trauma patients receiving lipid-based TPN. No significant differences in urinary carnitine excretion were noted between groups. We conclude that the use of lipids in the TPN of trauma patients leads to an alteration in plasma carnitine metabolism. *Am J Clin Nutr* 1988;48:1400–2.

KEY WORDS Carnitine, trauma, total parenteral nutrition, plasma carnitine, urinary carnitine

Introduction

Carnitine is a naturally occurring compound involved in mammalian energy metabolism. Its functions include facilitation of mitochondrial long-chain fatty acid oxidation, elimination of toxic metabolites of acyl CoA excess, modulation of the free CoA to acyl CoA ratio, and intercompartmental shuttling of energy substrates (1).

Carnitine is normally derived from dietary intake of animal products or by endogenous synthesis. Endogenous synthesis requires the essential amino acids lysine and methionine to form trimethyllysine. Trimethyllysine is then metabolized to carnitine via four enzymatic steps, the last of which, γ-butyrobetaine hydroxylation, occurs only in the liver or kidney in humans (2, 3). Skeletal and cardiac muscle contain the highest concentration of carnitine but depend on transport mechanisms via the plasma to replenish their stores.

In humans exogenous intake or endogenous synthesis in the liver or kidney is usually sufficient to meet metabolic needs. However, in certain clinical conditions abnormalities in carnitine metabolism have been described. Both surgical and burn patients show increased urinary excretion of carnitine relative to control subjects (4–6). Low tissue levels of carnitine were found in patients on hemodialysis (7) and low plasma levels were reported in patients with protein-calorie malnutrition (8). In our laboratory we (9) found a negative arterial-venous difference or a net loss of carnitine across the skeletal muscle in stressed, critically ill patients. Borum (10) suggested that carnitine may be a conditionally essential nutrient and that supplementation may be required for the metabolically stressed, critically ill patient. Currently, no enteral or parenteral nutritional supplements contain carnitine. Preliminary work from our laboratory with a small number of patients indicated that levels of plasma carnitine may be dependent on the total parenteral nutrition (TPN) solution infused (A Davis, D Scholten, R Albrecht, unpublished observation). The purpose of this study was to determine the effects of changing fuel substrate mix on plasma carnitine in a group of multiply injured patients.

Methods

The study protocol was approved by the Butterworth Hospital Human Rights Committee before implementation. Informed consent was obtained from all patients enrolled in the study. Twenty-five consecutive patients with polytrauma who required intensive care were entered in this prospective randomized crossover study. Of the 25 patients originally entered, 5 patients failed to complete the study; 1 died and 4 were dropped because of protocol violations. Polytrauma features included closed head injury, one or more major extremity fractures, and postoperative intraabdominal or thoracic trauma. Patients with Addison disease, cirrhosis, or renal failure were excluded. Severity of stress was assessed using the Abbreviated Index Severity Scale score (11). All patients had prestudy oxygen consumption indices calculated from data obtained either from pulmonary artery catheter sample studies (11 of 20 pa-

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Received October 19, 1987.

Accepted for publication January 27, 1988.

Am J Clin Nutr 1988;48:1400–2. Printed in USA.

TABLE 1
Plasma carnitine concentrations in trauma patients*

	Group 1 0% Lipid, 19% BCAA	Group 2 0% Lipid, 44% BCAA	Group 3 30% Lipid, 19% BCAA	Group 4 30% Lipid, 44% BCAA
			μmol/L	
Free carnitine	29.7 ± 3.3	28.9 ± 3.4	36.1 ± 4.6†	37.4 ± 4.1†
Short-chain acyl carnitine	7.2 ± 1.5	6.1 ± 0.7	12.7 ± 1.3†	12.0 ± 1.2†
Long-chain acyl carnitine	4.0 ± 0.4	4.4 ± 0.3	4.7 ± 0.9	5.1 ± 0.8
Total carnitine	40.4 ± 4.1	41.6 ± 3.8	52.9 ± 6.2†	55.9 ± 5.0†

* $\bar{x}$ ± SEM; n = 10 for all groups.
† Significant effect of lipid ($p < 0.05$).

tients) or by indirect calorimetry with the Beckman metabolic cart (Sensormedics, Anaheim, CA) (9 of 20 patients).

A factorial design was used by which the patients were randomized to receive one of four TPN solutions. Groups 1 and 2 (n = 10) were given 100% carbohydrate (CHO)-based TPN with no lipid provided as nonprotein calories. Groups 3 and 4 (n = 10) were given lipid-based TPN in which 30% of the nonprotein calories were provided by 20% Intralipid® (Kabivitrum, San Francisco, CA). The protein substrate had 19% branched-chain amino acids (BCAA) for groups 1 and 3 (Travasol®, Travenol Laboratories, Deerfield, IL) and 44% BCAA for groups 2 and 4 (Freamine HBC®, American McGaw Laboratories, Irvine, CA). Percentage BCAA was given as a percent of total amino acids. Total nonnitrogen calories were provided at a rate of 30 $cal \cdot kg^{-1} \cdot d^{-1}$. All solutions were isonitrogenous (0.24 $g\ N \cdot kg^{-1} \cdot d^{-1}$) and isovolemic. All patients received standard additions of trace elements, minerals, and vitamins. Daily adjustments were made in quantities of electrolytes and supplemental fluid as appropriate. Patients received nothing by mouth during the study period.

The study was conducted in two parts over 8 d. Patients were first randomized to one of the four TPN solutions. Within the CHO- or lipid-based groups patients were further randomized as to the order in which the two solutions were administered. After an equilibration period of 2 d, patients were studied on days 3 and 4. On day 5, patients were crossed over within the CHO- or lipid-based group to the opposite protein substrate. After 2 d equilibration the patients were studied on days 7 and 8.

On study days femoral arterial blood samples were obtained. Plasma samples were analyzed for total carnitine, free carnitine, short-chain acyl carnitine, and long-chain acyl carnitine. Carnitine was measured as described by Cederblad and Linstedt (12) and Bohmer et al (13), as modified by Brass and Hoppel (14). Twenty-four-hour urine collection was analyzed for free carnitine and acyl carnitine. The mean values for the two study days were used in the statistical analyses.

Plasma and urinary carnitines were analyzed using the factorial analysis of variance with a significance level of $p < 0.05$ (15). Differences in O_2 consumption and prestudy plasma carnitines were analyzed with the Student's t test.

Results

The 20 patients included 17 males and 3 females with an average age of 39.5 y. The median Abbreviated Injury Severity Scale (AIS) score was 35. Patients in groups 1 and 2 had a prestudy O_2 consumption index of 150.3 ± 13.7 whereas those in groups 3 and 4 had a value of 148.4 ± 31.6 ($\bar{x}$ ± SEM; $mL \cdot min^{-1} \cdot m^{-2}$). There were no statistically significant differences in the O_2 consumption indices between groups.

Prestudy values for patients in groups 1 and 2 for plasma free carnitine, short-chain acyl carnitine, and long-chain acyl carnitine were 39.1 ± 5.0, 14.0 ± 2.6, and 5.5 ± 0.8 μmol/L ($\bar{x}$ ± SEM), respectively. The corresponding values for patients in groups 3 and 4 were 43.0 ± 4.1, 7.1 ± 1.1, and 6.4 ± 0.8 μmol/L, respectively. The values for short-chain acyl carnitine were significantly different.

The study results of plasma carnitine analyses are shown in **Table 1.** There were statistically significant elevations of plasma free carnitine, short-chain acyl carnitine, and total carnitine in groups 3 and 4 (lipid-based TPN) as opposed to groups 1 and 2 (CHO-based TPN). Urinary excretion of carnitine (**Table 2**) was markedly increased in all four groups compared with urinary carnitine excretion of individuals on a low-carnitine diet (16). There were no statistically significant differences between groups.

Discussion

The widespread use of TPN and enteral products, none of which contain carnitine, has led investigators to question whether carnitine supplementation during nutritional support of certain patient groups should be implemented (10). Adults can synthesize carnitine in adequate amounts in liver and kidney from endogenous trimethyllysine. However, the hypermetabolic injured or septic patient may be at risk of developing a carnitine deficiency because of increased carnitine excretion, decreased synthesis, or increased requirements. Border et al (17) studied the relationship between infection and carnitine in a canine sepsis model and noted a decrease in skeletal muscle free carnitine 2 wk following the septic insult. Worthley et al (18) reported a septicemic patient on long-term TPN who developed an apparent carnitine deficiency.

In this study we measured the effects of changing the fuel substrate mix on plasma and urinary carnitine in multiply injured patients. A randomized crossover design was used to reduce the variability inherent to this type of study. All patients were similar in that they were

TABLE 2
Urinary carnitine excretion in trauma patients*

	Group 1 0% Lipid, 19% BCAA	Group 2 0% Lipid, 44% BCAA	Group 3 30% Lipid, 19% BCAA	Group 4 30% Lipid, 44% BCAA
			μmol/L	
Free carnitine	1123.6 ± 201.4	1283.8 ± 233.9	1430.8 ± 199.8	1312.0 ± 196.0
Acyl carnitine	404.4 ± 71.6	484.0 ± 97.4	641.6 ± 85.3	697.8 ± 168.0

* $\bar{x}$ ± SEM: n = 10 for all groups; $p > 0.05$ for ANOVA.

multiply injured and had similar degrees of stress as indicated by the elevated O_2 consumption values.

There were elevated levels of 24-h urinary carnitine excretion in all four groups (Table 2). These values are in distinct contrast to normal excretion levels of 100 μmol/d reported for patients on a carnitine-free diet (16). Our values are similar to those reported in two previous studies on stressed patients (5, 6).

The increased plasma carnitine in the lipid-based TPN groups may be due to an increase in intercompartmental shuttling of carnitine from areas of storage or synthesis (liver, kidney) to areas of higher metabolic need (skeletal, cardiac muscle). Borum (1) found that carnitine has the ability to transport metabolic energy from cell to cell or organ to organ in the form of acyl carnitine. This may be operative in these patients, especially those who received lipid-based TPN, to assist in β-oxidation.

The study was also designed to study the effect of BCAAs on N balance (to be published elsewhere) and carnitine metabolism. Bieber et al (19) delineated possible roles for carnitine in the metabolism of the BCAAs. Carnitine is also thought to have a role in the detoxification of excess acyl CoA by modulating the ratio of free CoA to acyl CoA via excretion of acyl carnitine. It is conceivable that administration of high concentrations of the BCAA in TPN could lead to an increase in the excretion of branched-chain acyl carnitines as expressed by the acyl carnitine fraction in urine. However, the level of BCAA in TPN had no significant effect on plasma or urinary carnitine fractions in our study. A recent study (20) of seven healthy volunteers compared the effects of modulating CHO and fat levels of meals on changes in plasma and urinary carnitine fractions. The study employed a high-CHO, low-fat diet and a low-CHO, high-fat diet with a crossover design. Although the study demonstrated that diet affects carnitine metabolism, as expressed by urinary and plasma carnitines, there was no significant effect of fuel mixture on plasma short-chain acyl carnitine during the study, as opposed to the findings of the present study. However, the meals in the cited study (20) contained carnitine whereas the TPN in the present study did not. Also, the patients in the present study were all trauma patients whereas the previous study was conducted with seven healthy male volunteers (20). Therefore, differences between the studies are not unexpected.

We conclude that the use of lipid in the TPN of trauma patients leads to an alteration in levels of plasma total and free carnitine and short-chain acyl carnitine. How these changes relate to tissue levels of carnitine or the functions of carnitine remains to be determined. The use of a high-BCAA formula in TPN had no significant effects on plasma or urinary carnitine fractions.

We thank Nancy Solis for sample collection and Laura VanWyk and Eric Hartfield for their technical assistance.

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