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Carnitine Balance and Effects of Intravenous L-Carnitine in Two Patients Receiving Long-Term Total Parenteral Nutrition

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ABSTRACT. Two patients requiring total parenteral nutrition for 34 and 39 months, had plasma and urinary carnitine assays and plasma lipid assays performed before and during intravenous administration of 400 mg (2500 μmol) of L-carnitine for 7 days, followed by 40 mg (240 μmol) daily continuously. One patient had generalized lethargy and weakness which resolved within the first 5 days of carnitine administration. The plasma-free carnitine levels in this patient rose significantly. The other patient was asymptomatic and while there was no significant change in the plasma-free carnitine levels during carnitine administration, this patient remained in positive carnitine balance throughout the study. There were no significant changes in plasma lipid levels in either patient. In adult patients requiring long-term total parenteral nutrition who are otherwise normal, intravenous L-carnitine may be required to supplement the patients endogenous carnitine production. (*Journal of Parenteral and Enteral Nutrition* **8**:717–719, 1984)

L-Carnitine is an essential part of the shuttle which involves carnitine acyltransferase[1] and translocase[2] transporting long-chain fatty acids from the cytosol across the mitochondrial membrane to the site of β oxidation.[3] Deficiency in carnitine has been reported to produce either a myopathic syndrome,[4] where there is normal plasma and low skeletal muscle carnitine concentrations, or a systemic syndrome[5] where both plasma and tissue concentrations of carnitine are low.

It is believed that carnitine deficiency is unlikely to occur in healthy individuals as 16 to 20 mg (100–125 μmol) can be synthesized endogenously daily in man and 60 to 75 mg (375–470 μmol) is present in the normal daily diet.[6] However, in premature infants and neonates receiving total parenteral nutrition (TPN) a marked reduction in plasma and tissue carnitine concentrations has been described when compared to infants receiving human milk or carnitine containing milk formulae.[7,8] Furthermore, in adult surgical patients requiring TPN[9,10] and in individual patients on long-term TPN[11] low levels of plasma and urinary carnitine concentrations have also been reported, suggesting that in the absence of dietary intake of carnitine, endogenous production of carnitine may be insufficient for daily human needs in patients on long-term TPN. In the absence of liver failure, however, a clinical syndrome of carnitine deficiency has yet to be reported in long-term TPN patients.

Following our report describing carnitine deficiency in a patient with hepatic insufficiency on long-term TPN,[12] we investigated two patients without biochemical evidence of hepatic insufficiency who had been receiving TPN for 34 and 39 months, to determine their carnitine balance and the effects of administering L-carnitine intravenously.

PATIENTS AND METHODS

Two patients requiring prolonged TPN were managed at home with intravenous nutrition administered during a 10 to 12-hr period throughout the night. Both patients had no oral intake apart from 200 to 700 ml of clear fluids daily. Intravenous dextrose provided the major caloric intake, and the nitrogen requirements, estimated from urinary urea and gastrointestinal protein losses, were supplied as Synthamin 17.* Sodium, potassium, phosphate, calcium, magnesium, acetate, zinc, copper, selenium, chromium, manganese, iodine, iron, vitamins A, D, E, K, C, and B group were given in amounts necessary to maintain normal physiological functions and serum levels. Intralipid 10% (500 to 1000 ml) was infused weekly to maintain the serum triene/tetrene ratio of less than 0.2. Hepatic function before and during the carnitine administration in both patients was normal as assessed from plasma aspartate amino transferase, lactic acid dehydrogenase, alkaline phosphatase, and conjugated and total bilirubin levels measured using a sequential multiple analyzer with computer (Technicon Instruments Corporation, Tarrytown, NY).

The patients clinical status, caloric intake, and nitrogen intake are shown in Table I. The clinical symptoms of lethargy and weakness in patient 1 had been present for 6 months before the administration of carnitine. Patient 2 was asymptomatic. L-carnitine 400 mg (2500 μmol) of L-carnitine administered daily continuously. Plasma free-, short-, and long-chain acyl carnitine, urinary free-, short-chain acyl, and total acid soluble carnitine were measured for 3 days prior to administration of carnitine and on the 4th, 5th, 6th, and 7th day of administration of 400 mg (2500 μmol) of L-carnitine and every 3rd day for 2 wk following the 1st wk of daily

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* Synthamin 17 contains per liter: Leucine 47.3 mmol, iso-leucine 36.6 mmol, valine 39.2 mmol, lysine 31.8 mmol, phenylalanine 37.5 mmol, methionine 38.9 mmol, tryptophan 8.8 mmol, threonine 35.3 mmol, arginine 59.7 mmol, histidine 28.4 mmol, alanine 233.5 mmol, glycine 277 mmol, proline 36.5 mmol, and tyrosine 2.2 mmol.

TABLE I
Clinical condition, caloric and nitrogen intake in the two long-term TPN patients

Patient	Disease	Clinical status	Duration of T.P.N.	Age	Sex	Wt	g nitrogen as Synthamin 17	Nonnitrogen calories as dextrose
			mo	*yr*		*kg*		
1	Scleroderma of GIT with surgical excision of all of small bowel	Generalized lethargy and weakness; sleeping 14–16 hr/day; a day; feeling continually cold	39	61	F	51	10	**1620**
2	Chronic idiopathic intestinal pseudoobstruction	No symptoms	34	24	F	60	12.1	**1940**

administration of 40 mg (250 μmol) of L-carnitine. This collection regime was based on our previous studies[12] in order to ensure stable plasma and urinary carnitine concentrations at each administration rate. Both patients consented and were informed that we would be studying a "food additive" which was to be included in their daily infusion; they were not informed as to its possible clinical effects.

Plasma lipids were measured on two occasions before the administration of L-carnitine and during the 1st wk of the study, then weekly during the next 3 wk. Venous blood samples were collected just prior to the administration of intravenous nutrition.

Plasma and urinary samples were treated with an equal volume of 15% (w/v) $HClO_4$ and centrifuged at 1500 x *g* in a bench centrifuge. In the case of the plasma samples, the resulting protein pellets were washed twice with a volume of 6% (w/v) $HClO_4$, twice that of the plasma volume, in order to remove trapped free- and short-chain acyl carnitine. Failure to observe this washing procedure results in an overestimation of long-chain acyl carnitine.

The washed protein pellets and acid supernatants were then processed according to the method of Brass and Hoppel[13] prior to the determination of free-, short-chain acyl and long-chain acyl carnitine by the method of Parvin and Pande[14] as modified by Pande and Parvin.[15] Serum total cholesterol was measured by the method of Richmond[16] and triglycerides were measured by the method of Bucolo and David.[17] The normal values for our laboratory were 4.0 to 7.0 and 0.5 to 1.9 mmol/liter, respectively, for total serum cholesterol and serum triglycerides.

Results were analyzed for statistical significance using Students *t*-test.

RESULTS

Prior to carnitine administration values for free- and short-chain acyl carnitine were low in both patients, ie, 33.2, 4.6 and 31.7, 2.6 μmol/liter respectively, compared with the values of 49.8 ± 1.3 and 6.6 ± 1.0 (means ± SEM) for free- and short-chain acyl carnitine estimated from normal patients. Both patients had normal serum levels of long-chain acyl carnitine, ie, 3.1 and 2.6 μmol/liter, respectively, compared with the value of 2.6 ± 0.2 (mean ± SEM) for long-chain acyl carnitine estimated in normal patients.

Before carnitine administration the 24-hr urinary mean free and total acid soluble carnitine values were 22, 87 μmol and 40, 81 μmol for patients 1 and 2, respectively, (Table II) and were low in comparison to published reports of normal daily free carnitine excretion [175 ± 81 (SD) μmol][19] and daily total acid soluble carnitine (239 ± 56 μmol).[20]

In patient 1 during the week of daily administration of 400 mg (2500 μmol) of L-carnitine, mean values of plasma-free, short-chain acyl, and long-chain acyl carnitine from the 4th to 7th day increased to 62.5, 6.6, and 2.5 μmol/liter, respectively, and during the infusion of 40 mg (250 μmol) of L-carnitine per day, plasma-free carnitine values remained elevated (Table III). The 24-hr urinary mean total acid-soluble carnitine values measured during the 4th to 7th day of the daily administration of 400 mg (2500 μmol) of L-carnitine indicated that after 3 days almost all of the L-carnitine was being excreted in the urine (2420 μmol/day). During the administration of 40 mg (250 μmol) of L-carnitine per day, a significant negative carnitine balance occurred during the 2-wk measurement period as a mean value of 479 μmol/day of urinary total acid soluble carnitine was recorded (Table II).

In patient 2 during the 7-day period of daily administration of 400 mg (2500 μmol) of L-carnitine, mean values of the plasma free; short-chain acyl and long-chain acyl carnitine from the 4th to the 7th day increased to 42.5, 10.1, and 7.8 μmol/liter, respectively (Table III). The 24-hr urinary mean total acid-soluble carnitine value of 1570 μmol measured during the 4th to 7th day of the daily administration of 400 mg (2500 μmol) of L-carnitine and the value of 175 μmol during the daily infusion of 40 mg (250 μmol) of L-carnitine indicated that approximately half of the infused L-carnitine was being retained during both periods (Table II).

The lethargy and weakness experienced by patient 1 resolved by the 5th day of carnitine administration. The patient, instead of requiring 14 to 16 hr of sleep, was now awake after 8 to 10 hr and able to manage household duties of preparing meals, tidying the house, and attending the supermarket, whereas before she would remain in a chair watching television for most of the day. Furthermore the patient remarked that she suddenly felt warmer whereas previously she had been feeling continually cold despite the ambient conditions. Patient 2 experienced no clinical change throughout the period of L-carnitine infusion. There was no significant change in the serum total cholesterol or triglyceride levels in either patient (Table I).

TABLE II
24-Hr urinary excretion of carnitine[a]

Patient	Carnitine fraction	Before L-carnitine administration	L-carnitine administration	
			400 mg (2500 μmol)/day	40 mg (250 μmol)/day
1	Free	22 ± 0.3 (3)	1920 ± 43 (4)[b]	353 ± 38 (6)[b]
	Short-chain acyl	71 ± 7 (3)	508 ± 46 (4)[b]	143 ± 22 (6)
	Total acid-soluble	87 ± 6 (3)	2420 ± 77 (4)[b]	479 ± 44 (6)[b]
2	Free	40 ± 20 (3)	1290 ± 157 (4)[c]	112 ± 14 (4)[d]
	Short-chain acyl	41 ± 9 (3)	304 ± 17 (4)[b]	63 ± 14 (4)
	Total acid-soluble	81 ± 28 (3)	1570 ± 132 (4)[b]	175 ± 22 (4)[d]

[a] The figures are means ± SEM with the number of samples in parentheses and those significantly different from figures before L-carnitine administration are indicated as follows: [b] $p < 0.001$; [c] $p < 0.01$; [d] $p < 0.05$.

TABLE III
Plasma carnitine and serum lipid values before and during L-carnitine administration[a]

Patient	Carnitine fraction	Before L-carnitine administration	L-carnitine administration	
			400 mg (2500 μmol)/day	40 mg (250 μmol)/day
		μmol/liter		
1	Free	33.2 ± 0.6 (3)	62.5 ± 2.3 (4)[b]	59.8 ± 2.8 (6)[b]
	Short-chain Acyl	4.6 ± 1.6 (3)	6.6 ± 2.7 (4)	5.8 ± 1.3 (6)
	Long-chain Acyl	3.1 ± 0.1 (3)	2.5 ± 0.3 (4)	3.4 ± 0.2 (6)
2	Free	31.7 ± 3.3 (3)	42.5 ± 3.6 (4)	26.6 ± 0.8 (6)
	Short-chain Acyl	2.6 ± 0.8 (3)	10.1 ± 2.5 (4)	8.7 ± 1.4 (6)[c]
	Long-chain Acyl	2.8 ± 0.7 (3)	7.8 ± 1.5 (4)[c]	3.1 ± 0.1 (6)
1	Triglycerides	1.8 ± 0.1 (2)	1.9 ± 0.1 (2)	1.8 ± 0.1 (3)
	Total cholesterol	3.8 ± 0.05 (2)	3.8 ± 0.1 (2)	3.9 ± 0.04 (3)
2	Triglycerides	1.1 ± 0.04 (2)	0.8 ± 0.03 (2)	1.0 ± 0.08 (3)
	Total cholesterol	2.8 ± 0.1 (2)	2.4 ± 0.1 (2)	2.2 ± 0.2 (3)

[a] The figures are means ± SEM with the number of samples in parentheses and those significantly different from figures before L-carnitine administration are indicated as follows: [b] $p < 0.001$; [c] $p < 0.05$.

DISCUSSION

Using conventional amino acid, dextrose, and lipid solutions, patients receiving TPN have their dietary intake of carnitine reduced essentially to zero. While in healthy patients 16 to 20 mg/day (100 – 125 μmol) of L-carnitine may be synthesized endogenously[6] it is not known whether this amount is adequate to satisfy daily adult human requirements.

Low levels of serum and urinary carnitine have been reported in adult surgical patients requiring TPN for longer than 20 to 40 days[9] and in home TPN patients,[11] however, clinical evidence of carnitine deficiency has not been described in patients requiring long-term TPN in the absence of hepatic failure.[20]

The two patients described both had normal liver function studies. The recorded low plasma and urinary carnitine values and the resolution of clinical symptoms of lethargy and weakness in patient 1 and the continuous positive balance of carnitine in patient 2 indicated that endogenous production of carnitine may not have been adequate for normal daily requirements in these two patients. In both patients there was no evidence of acidosis,[21] cardiomyopathy,[22] or, with Carnitine repletion, change in plasma lipids as has been previously described.

It would seem that to guarantee normal carnitine balance in patients receiving long-term TPN, supplementation of the normal endogenous production of carnitine by administering 40 mg (250 μmol) of L-carnitine intravenously daily may be required.

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