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Carnitine Deficiency with Hyperbilirubinemia, Generalized Skeletal Muscle Weakness and Reactive Hypoglycemia in a Patient on Long-term Total Parenteral Nutrition: Treatment with Intravenous L-Carnitine

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ABSTRACT. Low levels of plasma carnitine and reduced urinary carnitine excretion with persistently elevated plasma bilirubin levels, reactive hypoglycemia and generalized skeletal muscle weakness are described in a patient requiring long-term total parenteral nutrition (TPN). Intravenous administration of L-carnitine at 400 mg/day for 7 days and subsequently a maintenance dose of 60 mg/day corrected the plasma carnitine deficiency and reactive hypoglycemia and was associated with a return to normal plasma bilirubin levels and a restoration of skeletal muscle strength.

L-Carnitine is required for the transport of activated long chain fatty acids into the matrix compartment of mitochondria of tissues for subsequent oxidation.[1] In carnitine deficiency, fatty acid oxidation is reduced and fatty acids may be diverted into triglyceride synthesis, particularly in the liver. Also, there is a readjustment of the balance between carbohydrate and fat metabolism and glycolysis is increased.

Carnitine deficiency may occur as a genetically determined metabolic defect or as an acquired disorder associated with severe nutritional protein deficiency and cirrhosis due to a diminished endogenous production and exogenous intake of carnitine.[2] It may also occur due to an excess dialysate loss of carnitine in patients requiring hemodialysis for chronic renal failure.[3] However, in normal patients, carnitine deficiency is rare, since the daily requirement may be met by endogenous hepatic synthesis from methionine and lysine,[4] in addition to the dietary intake.

Patients receiving parenteral nutrition may develop hepatic fatty infiltration with liver function tests indicative of cholestasis.[5] Reactive hypoglycemia may also occur with the abrupt cessation of the parenteral nutrition infusion.[6] These clinical manifestations may also occur with carnitine deficiency.[2] Neonatal and premature infants when receiving TPN show a marked reduction in plasma and tissue carnitine when compared to infants receiving human milk or carnitine-containing milk formulae.[7, 8] To date, however, carnitine deficiency in adults receiving TPN has not been described.[9]

We have investigated the possibility of carnitine deficiency in an adult male patient, who had been maintained on TPN for 1 year and who had a persistently elevated plasma bilirubin concentration generalized skeletal muscle weakness, and reactive hypoglycemia.

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CASE REPORT

A 41-year-old, previously fit man was admitted to the intensive care unit with gas gangrene of the anterior abdominal wall and *Clostridium welchii* septicemia developing 24 hr after a laparotomy for small bowel obstruction.

The patient was anuric and in shock. Intravenous penicillin, (4×10^6 U four times hourly) and Isoprenaline (6 μg/min) were administered and the patient underwent an operation to excise the necrotic anterior abdominal wall, leaving the peritoneal cavity and underlying bowel exposed. Postoperatively he required hemodialysis for 6 weeks and intermittent positive pressure ventilation for 4 weeks. Although split skin grafts were placed directly onto the exposed bowel wall to cover the anterior abdominal surface, 6 small bowel fistulae developed, necessitating prolonged intravenous alimentation to maintain normal nutrition. During this period he also developed a cholestatic jaundice with peak plasma values of total bilirubin 555 μmol/liter (normal; 6–24 μmol/liter), conjugated bilirubin 510 μmol/liter (normal; 1–4 μmol/liter), aspartate amino transferase 270 U/liter (normal; 5–40 U/liter), and lactate dehydrogenase 407 U/liter (normal; 110–230 U/liter), occurring 6 weeks postoperatively. The only medications the patient received during this time were parenteral vitamins, penicillin, gentamycin, and lincomycin.

Abdominal ultrasound scans revealed an enlarged liver without evidence of cholelithiasis or enlarged bile ducts. Serum tests to detect hepatitis B surface antigen and antibody, infectious mononucleosis, toxoplasmosis, and cytomegalic inclusion virus were also negative. The hepatic failure was thought to be due to the severe abdominal sepsis and TPN, producing hepatic steatosis and a predominantly cholestatic jaundice.

Total parenteral nutrition was required throughout his hospital stay and was administered during a 12-hr period at night in 4.5 liters of fluid. 2,600 non-nitrogen calories were given as dextrose; 18 gm of nitrogen were given as

TABLE I
Plasma metabolite concentrations for the patient before and during L-carnitine administration

Metabolite	Normal values[a]	Before L-carnitine administration	L-carnitine administration	
			400 mg/day	60 mg/day
		mmol/liter		
Glucose	4–6	3.8 ± 0.3 (7)		5.6 ± 0.6 (5)[b]
3-Hydroxybutyrate	0.1–0.18	0.042 ± 0.003 (7)		0.037 ± 0.006 (8)
Triglycerides	0.5–1.9	1.6 ± 0.6 (5)		
Total cholesterol	4.0 – 7.0	4.4 ± 0.1 (5)	4.2 ±	
		μmol/liter		
Free carnitine	38.9 ± 6.7	19.5 ± 0.8 (7)	62.1	
Short chain acyl-carnitine	3.9 ± 1.8	1.8 ± 0.5 (7)	11.6	
Long chain acyl-carnitine	10.4 ± 2.6	7.4 ± 0.4 (7)	24.2 ±	
Total carnitine	52.0 ± 6.7	28.6 ± 1.4 (7)	97.8 ± 3.9 (9)	44.0 ±
Conjugated bilirubin	1–4	47 ± 3.7 (7)	14 ± 0.3 (3)[c]	7 ±
Total bilirubin	6–24	65 ± 5.4 (7)	25 ± 1.5 (3)[c]	15 ±

[a] Values are means ± SEM with the number of samples in brackets.
[b] Significantly different from the figures before L-carnitine administration at $p < 0.01$ level.
[c] Significantly different from the figures before L-carnitine administration at $p < 0.001$ level.

800 ml of Synthamin-17®‡ and 50 mmole lysine, 60 mmole leucine, 40 mmol isoleucine, 40 mmole valine, and 30 mmole histidine. The latter five amino acids were added to produce a normal fasting serum amino acid profile. Sodium, potassium, phosphate, calcium, magnesium, acetate, zinc, copper, selenium and vitamins A, D, E, K, folic acid, B_{12}, C, and B group were given in amounts necessary to maintain normal physiological functions and serum levels. Intralipid-10% (500 to 1000 ml) were infused each week to maintain the triene/tetrene ratio < 0.2. Intravenous lipid solutions were not given daily, since the patient developed an elevated temperature and rigors each time intralipid-10% was infused.

The patient underwent a further operation to close the six abdominal fistulae, although two subsequently reopened. Twelve months after the initial operation the patient was discharged from the hospital to manage his parenteral nutrition and convalescence at home. However, he remained icteric with persistently elevated plasma bilirubin levels (Table I), complaining of symptomatic reactive hypoglycemia with cessation of the TPN (the plasma glucose on one such occasion was 0.5 mmol/liter) and generalized muscular weakness. The latter confined him to bed throughout most of the day.

Plasma carnitine measurements revealed markedly low levels of free-, long and short chain acyl carnitine and urinary carnitine excretion was less than normal. 400 mg of L-carnitine was administered intravenously daily for 7 days followed by 40 mg/day for 3 weeks and thereafter 60 mg/day.

Plasma-free, short and long chain acylcarnitine, urinary free, short chain acyl- and total acid-soluble carnitine, plasma lipids, and three hydroxybutyrate were measured daily for 4 weeks and thereafter weekly. Plasma glucose, total, and conjugated bilirubin were measured twice weekly.

‡ Synthamin 17® contains per liter: leucine, 47.3 mmol; isoleucine, 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.

MATERIALS AND METHODS

Venous blood samples were collected just prior to the administration of the intravenous nutrition. Blood samples were also collected from 12 normal male subjects (aged 22–43 years) for the assay of plasma carnitine fractions.

Plasma and urinary carnitines were measured by the radio-enzymic method of Parvin and Pande,[10] with modifications as suggested by Pande and Parvin[11] and Snoswell and Henderson,[12] following separation of the plasma into various carnitine fractions according to the method of Brass and Hoppel.[13] Plasma glucose, total, and conjugated bilirubin were measured, using a sequential multiple analyser with computer (Technician Instruments Corporation, Tarrytown, NY). Total cholesterol was measured by the method of Richmond,[14] triglycerides were measured by the method of Bucolo and David,[15] and 3-hydroxybutyrate was measured by the method of Williamson et al.[16] Results were analyzed for statistical significance using Student's *t*-test.

RESULTS

The results shown in Table I indicate that prior to carnitine administration the patient had low plasma carnitine concentrations in comparison with plasma carnitine concentrations we estimated from 12 normal male subjects of 38.9 ± 6.7, 3.9 ± 1.8, 10.4 ± 2.6, and 52.0 ± 6.7 μmol/liter (mean ± SD) for free, short chain acyl, long chain acyl, and total carnitine, respectively. The [illegible] for plasma carnitine concentrations were also low, with respect to total acid-soluble carnitine (free plus short chain acyl) published for normal male patients 13 (SD) μmol/liter when assayed by a similar [illegible] ical method.[17] Also, the daily excretion of free carnitine of 44 μmol/day (Table II) during the period was considerably less than the value of 175 ± 81 (SD) μmol/day reported for normal males.

Following the daily administration of 400 mg of L-carnitine, plasma carnitine concentrations plateaued at higher values after 3 days (Fig. 1) indicating that this

TABLE II
Urinary excretion of carnitine in the patient

	Normal values[a]	Before L-carnitine administration	L-carnitine administration		
			400 mg/day[b]	40 mg/day	60 mg/day
			μmol/24 hr		
Free carnitine	175 ± 81[c]	44 ± 10 (3)	1170 ± 79 (4)	104 ± 15 (3)	141 ± 29 (2)
Short chain acyl-carnitine		77 ± 13 (3)	363 ± 66 (4)	101 ± 4 (3)	178 ± 18 (2)
Total acid-soluble carnitine	239 ± 56[c]	120 ± 7 (3)	1530 ± 52	205 ± 15 (3)	319 ± 47 (2)

[a] The figures shown are means ± SEM with the number of observations in brackets.
[b] The samples at 400 mg/day were collected between the 4th and 7th days of carnitine administration.
[c] From Reference 18.
[d] Total acid-soluble carnitine, free + short chain acyl-carnitine.
[e] From Reference 17.

time may have been required to saturate the extra cellular tissue space in the body. Subsequent administration of a maintenance dose of 40-mg L-carnitine/day resulted in the establishment of plasma carnitine concentrations nearer the normal values (Fig. 1). However, the daily excretion of total acid-soluble carnitine of 205 ± 15 μmol/day (Table II) was still slightly below the normal daily excretion for males of 239 ± 56 (SD) μmol/day.[17] The maintenance dose was therefore increased to 60 mg/day for 3 weeks and maintained at that level thereafter. This intake value is very similar to the mean daily excretion value of 59.3 mg reported for a larger population of males.[19] At this maintenance dose the total plasma carnitine concentration of 44 μmol/liter (Table 1) was in the normal range, although the concentration of the long chain acyl fraction of 14.4 μmol/liter was somewhat elevated with respect to normal values reported here and by Genuth and Hoppel.[20]

The administration of carnitine resulted in a reduction in the elevated plasma total and conjugated bilirubin to normal levels, although the serum 3-hydroxybutyrate, triglyceride, and total cholesterol levels remained unchanged (Table I).

With the maintenance dose of carnitine the plasma glucose also remained in the normal range and was significantly above that prior to carnitine administration (Table 1). Furthermore, the patient had no symptomatic episodes of hypoglycemia with cessation of his daily TPN infusion. The low plasma 3-hydroxybutyrate concentrations in this patient, both before and after carnitine administration, may be correlated with the elevated long chain acyl carnitine fraction (Table I) and may indicate some enzymic deficiency in the liver of the patient. During the first week of L-carnitine administration the patient began to improve clinically. He became ambulant and spent less and less time in bed throughout the day, gaining in strength and noting a sense of wellbeing that he had not had during the previous 12 months. This improved clinical status has now continued for 13 months on the maintenance carnitine infusion of 60 mg L-carnitine/day.

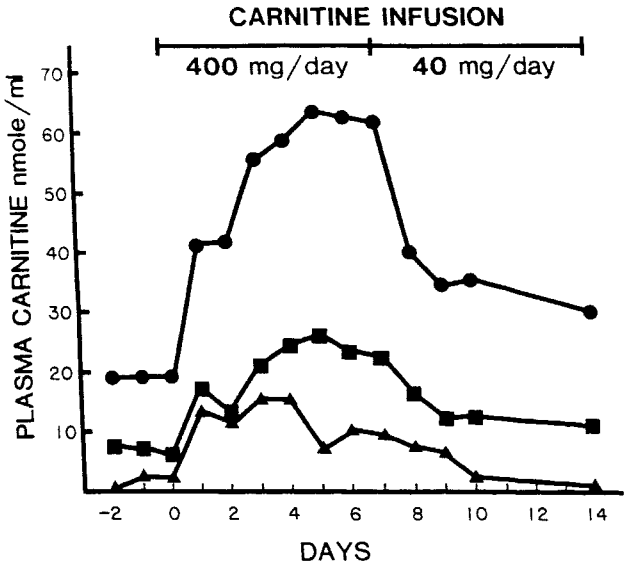

FIG. 1. The effect of L-carnitine administration on plasma carnitine concentrations in the patient. ●——●, free carnitine; ■——■, long chain acylcarnitine; ▲——▲, short chain acylcarnitine.

DISCUSSION

A defect in lipid metabolism with hepatic fatty infiltration and abnormal liver function tests often occurs in patients receiving parenteral nutrition.[3] Fundamentally the disturbance is due to an increased production, diminished utilization or defect in secretion of hepatic lipids, and each of these defects have been reported with intravenous alimentation. For example, extensive production of lipid occurs with excessive glucose administration, even in patients with high calorific requirements.[21] Furthermore, when glucose is administered continuously, the lipid so formed is unable to be mobilized easily, due to the persistent effect of insulin promoting lipogenesis and inhibiting lipolysis.[22, 23] Defective secretion of hepatic lipids has also been described with deficiencies of essential fatty acids,[24] choline and methionine deficiencies,[25] bacterial toxins,[26] abnormal metabolism of bile salts[27] and toxic effects of amino-acids and their metabolites.[28, 29] Diminished utilization of fatty acids for energy and ketone production are further insulin-induced effects.[30]

Since the transport of long chain fatty acids from the sites of activation in the cytoplasm to the sites of β-oxidation in the mitochondria requires carnitine and since there is competition between the pathways of β-oxidation and triglyceride formation for cytosolic-free fatty acids, carnitine deficiency enhances hepatic lipogenesis.[31, 32]

Carnitine deficiency is unlikely to occur in healthy individuals as 16–20 mg can be synthesized endogenously

daily in man and 60–75 mg is present in the normal diet.[33] Apart from the rare patient with a genetically determined biochemical defect of carnitine metabolism, and the patient with chronic renal failure with excessive loss of carnitine during hemodialysis, acquired carnitine deficiency has mainly been reported in patients with severe nutritional protein deficiency and malnourished cirrhotic patients, due to a defective endogenous synthesis and low dietary intake of carnitine.[2]

As synthesis of carnitine by intestinal microflora has not yet been described,[34] patients receiving TPN have their dietary intake of carnitine reduced essentially to zero. If they have hepatic dysfunction as well, then they may be unable to produce adequate amounts of carnitine for normal fatty acid metabolism. Moreover, if carnitine deficiency exists, then the hepatic dysfunction may be exacerbated due to excessive triglyceride deposition within the hepatocytes.

Low levels of carnitine have been reported in neonates and infants receiving TPN.[7, 8] In experimental studies, rats fed parenterally have a reduced incidence of hepatic steatosis and an improved N_2 balance when their nutritional regimen is supplemented with carnitine.[35] In the patient we describe, the hepatic failure may have been induced by gross abdominal sepsis and TPN. However, the continuing presence of abnormal liver function, generalized weakness, and severe reactive hypoglycemia suggested an additional disorder.

Carnitine deficiency was suspected by the presence of low plasma and urinary levels and although plasma carnitine levels may not necessarily correlate with tissue carnitine levels,[36] severely depressed plasma levels observed in our patient were certainly suggestive of depletion. Plasma values were corrected by L-carnitine administration, initially 400 mg/day for 7 days and subsequently 60 mg/day continuously. The addition of carnitine was associated with a return to normal of plasma bilirubin levels, absence of reactive hypoglycemia and improved muscle strength. We did not observe any evidence of cardiomyopathy,[37, 38] acidosis,[2, 39] or, with carnitine repletion, change in plasma lipids[40] or ketones,[19] as has been previously reported.

In patients requiring TPN hepatic dysfunction may develop, diminishing endogenous synthesis of carnitine. If carnitine deficiency is present it will lead to hepatic steatosis, which will, in turn, exacerbate the presence of hepatic dysfunction. Thus, it would seem that for patients requiring long-term TPN, carnitine addition may be necessary to ensure normal fatty acid metabolism.

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