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Muscle Carnitine Repletion by Long-Term Carnitine Supplementation in Nephropathic Cystinosis

WILLIAM A. GAHL, ISA M. BERNARDINI, MARINOS C. DALAKAS, THOMAS C. MARKELLO, DONNA M. KRASNEWICH, AND LAWRENCE R. CHARNAS

Section on Human Biochemical Genetics [W.A.G., I.M.B., T.C.M., D.M.K.] and Unit on Neurogenetics [L.R.C.], Human Genetics Branch, National Institute of Child Health and Human Development; and Section on Neuromuscular Diseases [M.C.D.], Medical Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Maryland 20892

ABSTRACT. The renal tubular Fanconi syndrome of children with nephropathic cystinosis causes plasma and musle carnitine depletion. L-Carnitine replacement therapy for up to 18 mo has previously been shown to normalize plasma but not muscle carnitine levels. We treated six cystinosis patients, aged 1 to 4 y, with a mean dosage of 92 mg L-carnitine/kg/d given every 6 h for an average of 62 mo. Despite fractional excretions of free carnitine ranging from 55 to 108%, plasma-free and total carnitine concentrations were maintained at or above normal levels. At the end of the carnitine replacement period, the six children had muscle-free carnitine values ranging from 16.0 to 28.0 nmol/mg noncollagen protein compared with values of 3.0 to 11.4 for cystinosis children not supplemented with carnitine [normal, 22.7 ± 5.0 (SD) nmol/mg protein]. Total muscle carnitine values were also normalized by L-carnitine replacement. The monthly increase in total body creatinine production, a measure of muscle mass, was higher (p = 0.036) in children with normal plasma free carnitine concentrations (3.4 ± 0.9 mg/d) than in children with low plasma free carnitine (2.3 ± 0.7 mg/d). No serious side effects, such as severe diarrhea, were observed. We conclude that oral L-carnitine replacement can normalize muscle carnitine content in children with cystinosis. (*Pediatr Res* 34: 115–119, 1993)

Carnitine, or β-hydroxy-trimethylaminobutyric acid, mediates the transport of long-chain fatty acids into the mitochondrial matrix for subsequent catabolism by β-oxidation to produce energy (1, 2). This process is essential for skeletal muscle (3), which serves as a large reservoir for carnitine (4) but cannot itself synthesize this molecule. Rather, carnitine is synthesized in the liver, kidney, and brain from methionine and lysine (1), and is also supplied by gastrointestinal absorption after the ingestion of meats and milk. Carnitine exists either free or esterified to fatty acids, primarily as acetylcarnitine (1).

In normal individuals, free carnitine is filtered by renal glomeruli and is 97% reabsorbed by the kidney tubules (5). Patients with renal Fanconi syndrome, however, fail to reabsorb carnitine (5, 6) along with other small molecules including water, glucose, amino acids, phosphate, calcium, magnesium, sodium, potassium, and bicarbonate. Typically, free carnitine is only 67% reabsorbed in Fanconi syndrome, resulting in low plasma carnitine levels (5). Because the circulation provides the only conduit for supplying carnitine to muscle, this results in low muscle carnitine levels (5, 7).

Nephropathic cystinosis, a lysosomal storage disease characterized by renal failure at approximately 10 y of age, is the most common identifiable cause of renal tubular Fanconi syndrome in children (8, 9). Before receiving a renal transplant, patients with cystinosis have plasma free carnitine concentrations that average 11.7 ± 4.0 (SD) μM (normal, 42.0 ± 9.0 μM) and muscle free carnitine levels averaging 8.3 ± 1.8 nmol/mg of noncollagen protein (normal, 22.7 ± 5.0 nmol/mg) (5, 7). The muscle carnitine content of children with cystinosis does not appear to vary with age between 2 and 10 y (7).

Oral carnitine supplementation rapidly normalizes plasma free carnitine concentrations in children with cystinosis. However, carnitine therapy did not appear to correct muscle carnitine depletion even after 18 mo, although the results were inconsistent from one individual to another (7). We now present the results of 5 y of carnitine replacement in six cystinosis patients, initially treated at 1 to 4 y of age, with muscle carnitine levels and measurements of total body creatinine production.

MATERIALS AND METHODS

Subjects. Nephropathic cystinosis was diagnosed based upon the presence of corneal crystals, renal tubular Fanconi syndrome, and elevated leucocyte cystine levels (8, 9). Twenty-three affected children aged 0 to 12 y were included in this study, 14 listed in Table 1 and nine additional patients in Table 2. Only patients 1 to 6 received long-term oral L-carnitine therapy with consistently high plasma free carnitine concentrations. All 23 patients had their original, functioning kidneys, with serum creatinine concentrations ranging from 0.5 to 1.7 mg/dL (44–150 μmol/L). All received replacement of renal losses as needed, generally with phosphate, potassium, and citrate for alkalinization (8, 9). The cystine-depleting agents, cysteamine (β-mercaptoethylamine) (10) and phosphocysteamine (11), which have proven efficacy in maintaining renal function and enhancing growth in cystinosis (12, 13), were administered to all patients at a dosage of 1.3 to 1.95 g of free base/m^2/d divided every 6 h. Affected children were examined as inpatients at the National Institutes of Health Clinical Center every 4 to 6 mo under a protocol approved by the National Institute of Child Health and Human Development Institutional Review Board. Two 24-h urines were routinely collected for creatinine and carnitine during each admission. Informed consent was obtained from all patients or their parents.

Liquid L-carnitine (100 mg/mL) was a product of Sigma-Tau, Inc. (Gaithersburg, MD). Carnitine was administered at approx-

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Correspondence and reprint requests: William A. Gahl, M.D., Ph.D., National Institutes of Health, Building 10, Room 9S-242, Bethesda, MD 20892.

Table 1. *Muscle carnitine values in cystinosis patients treated and not treated with oral L-carnitine*

Patients*	Age (mo)	L-carnitine replacement: Mean dosage (mg/kg/d)	L-carnitine replacement: Duration (mo)	Muscle carnitine (nmol/mg protein): Free	Muscle carnitine (nmol/mg protein): Total
Treated					
1	69	83	54	16.0	20.0
2	81	97	61	19.3	25.4
3	83	84	56	16.4	26.2
4	85	98	62	20.6	32.9
5	91	111	59	28.0	34.1
6	136	78	79	17.9	23.8
Mean	91	92	62	19.7	27.1†
SD	23	12	9	4.4	5.4
Not treated					
6‡	57			11.4§	15.9
7	67			10.0§	14.8
8	74			7.7§	10.1
9	79			7.9§	11.7
10	80			6.8§	7.4
11	109			8.7§	11.5
12	114			8.8§	9.1
13	120			9.9	12.9
14	143			3.0	4.4
Mean	94			8.2	10.9
SD	29			2.4	3.6
Normal					
Mean				22.7	27.9
SD				5.0	7.7
n				6	6

* The mean plasma free carnitine of the treated patients was 54 ± 14 (SD) μM compared with 14 ± 5 μM for the untreated group (normal, 42 ± 9.0 μM).

† Different from "not treated" mean at $p < 0.001$.

‡ Before L-carnitine replacement.

§ These values have been previously reported (7).

imately 100 mg/kg/d (0.62 mmol/kg/d) in divided doses given every 6 h.

Materials. 1-^{14}C-acetyl CoA (50 mCi/mmol) was obtained from New England Nuclear (Boston, MA) and from ICN Pharmaceuticals (Irvine, CA, and Plainview, NJ), which also supplied sodium tetrathionate. Ultrapure Tris was from Boehringer-Mannheim Biochemicals (Indianapolis, IN), and AG1-X8 resin, 200- to 400-mesh, was from Bio-Rad Laboratories (Richmond, CA). Acetyl CoA, L-carnitine, and carnitine acetyltransferase were products of Sigma Chemical Co. (St. Louis, MO).

Methods. Free and total carnitine in plasma and urine were assayed according to McGarry and Foster (14), as previously described (5). Fractional excretion of carnitine was calculated as 100× (urine carnitine × serum creatinine)/(serum carnitine × urine creatinine). Muscle carnitine was measured as described (15). Open or needle muscle biopsies, taken from the quadriceps muscle, were fresh-frozen in isopentane, cooled to −160°C in liquid nitrogen, and processed for oil-red-O staining, as described (16). Creatinine was assayed by a modification of the Jaffe reaction (17), and protein by the bicinchoninic acid method (18).

Statistics. Group comparisons used *t* test. Rates of increase of daily urinary creatinine excretion were determined by linear regression analysis.

RESULTS

Six children with cystinosis, ages 15, 20, 27, 23, 32, and 57 mo, had plasma free carnitine concentrations of 5 to 18 μM (normal, 42 ± 9 μM) before carnitine supplementation (Fig. 1*A*). Total carnitine concentrations varied between 5 and 29 μM (normal, 52.3 ± 11.4 μM) (Fig. 1*B*). Oral L-carnitine replacement was initiated at a mean dosage of 92 mg/kg/d for a mean duration of 62 mo (Table 1). Plasma free and total carnitine concentrations, which normalize within hours after the start of therapy (7), were maintained at or above normal levels in each patient throughout the treatment period (Figs. 1*A* and *B*).

Before carnitine replacement, the fractional excretion of free carnitine ranged from 21 to 38% in the six children subsequently treated (Fig. 2). Over the subsequent years of carnitine supplementation, the mean fractional excretion of free carnitine was maintained between 55 and 108%.

At the end of the period of carnitine replacement, the six patients had a mean age of 91 mo (range, 69–136 mo) and normal mean free and total carnitine levels in their muscle, *i.e.* 19.7 and 27.1 nmol/mg noncollagen protein, respectively (Table 1). Each individual child also had free and total muscle carnitine values within the normal range. This was in striking contrast to the muscle carnitine values in nine cystinosis patients, aged 57 to 143 mo, who never received carnitine; all had low muscle carnitines, with mean free and total carnitine levels of 8.2 and 10.9 nmol/mg noncollagen protein, respectively ($p < 0.001$).

One of the most objective measures of increased muscle mass and function is urinary creatinine excretion, because creatinine is a characteristic end-product of muscle metabolism. Therefore, we measured the monthly rate of increase in creatinine production, as gauged by 24-h urinary excretion, in a total of 15 cystinosis children (Table 2). These patients were selected based upon their ages, lack of renal failure, and mean plasma free carnitine values, which spanned a broad range from 8 to 71 μM. The patients were chosen without *a priori* knowledge of their rates of increase in urinary creatinine excretion. They were divided into two groups. In one group were the six children with low plasma free carnitine values (≤22 μM). In the other were the nine children with normal plasma free carnitine values (>30 μM), including patients 1 to 6 and two patients (21 and 22) who did not receive carnitine replacement. The mean ± SD monthly increase in creatinine excretion for the nine children with normal carnitines was 3.4 ± 0.9 mg/d. This was significantly greater than the mean ± SD (2.3 ± 0.7 mg/d) for the six children with low plasma free carnitine concentrations ($p = 0.036$). The two subgroups had similar mean ages and durations of follow-up.

Despite the normalization of muscle carnitine levels by carnitine supplementation, treated patients showed no reduction in the number of lipid droplets apparent on oil-red-O staining of their muscle biopsies (data not shown).

None of the children treated long-term with oral L-carnitine experienced any of the known side effects of therapy, including nausea, vomiting, diarrhea, or a fish-like odor to their breath and skin.

DISCUSSION

Carnitine deficiency in man can have a wide variety of causes, including inadequate dietary intake or gastrointestinal absorption (19), impaired hepatic synthesis (20), increased removal by hemodialysis (21, 22), deficient transport at the level of the plasma membrane (23–25) or inner mitochondrial membrane (26), excessive esterification by fatty acids that accumulate due to short-chain (27) or medium-chain (4) acyl-CoA dehydrogenase deficiency, binding by medications such as valproic acid (28) or pivalate (29), and inordinate renal losses (5, 6). Patients with carnitine deficiency involving the plasma, muscle, and liver may exhibit a cardiomyopathy or a Reye-like syndrome with encephalopathy and hypoglycemia (20, 24, 30, 31). Other patients, such as those with renal tubular Fanconi syndrome, have carnitine deficiency involving the plasma and muscle compartments; the liver, supplied by the portal circulation and by *de novo* synthesis, has not been demonstrated to be carnitine-deficient in these patients, although liver biopsies have not been performed.

Table 2. *Rate of increase in daily creatinine production for cystinosis children with different plasma free carnitine concentrations**

Patient	Age† (mo)	Creatinine Clearance† (mL/min/1.73 m²)	Carnitine therapy‡	Duration of follow-up (mo)	No. of visits	Mean plasma free carnitine (μM)	Monthly increase in daily creatinine production (mg)
Low carnitine							
15	114	28	N	64	11	8	1.4
16	116	26	N	61	9	12	3.3
17	56	33	N	43	9	13	2.8
18	48	43	N	46	13	14	1.8
19	158	53	N	92	11	16	2.3
20	140	16	N	67	13	22	2.4
Mean ± SD	105	33		62	11	14	2.3
	44	13		18	2	5	0.7
Normal carnitine							
21	103	39	N	59	15	30	4.8
22	100	39	N	51	11	31	2.1
23	77	51	Y	57	14	32	3.6
4	79	83	Y	47	12	36	4.5
3	81	67	Y	60	11	42	2.7
1	69	46	Y	54	12	47	2.9
5	91	72	Y	56	12	62	2.5
2	81	49	Y	50	12	64	3.1
6	136	40	Y	82	13	71	4.2
Mean ± SD	91	54		57	12	46	3.4§
	20	16		10	1	16	0.9

* Fifteen cystinosis children, on whom urinary creatinine data were available for at least 43 mo, were ordered according to their mean plasma free carnitine concentrations. The mean ages for patients with low and normal plasma carnitine values were 75 and 62 mo, respectively. Patients 1 to 6 are as listed in Table 1. For each patient, the rate of increase in daily creatinine excretion, based upon nine to 15 regular inpatient 24-h urine collections per patient, was calculated by linear regression analysis and expressed as a monthly increase, in mg. For 13 of the 15 patients, the data fit a linear model, with correlation coefficients between 0.67 and 0.95. Normal daily creatinine excretion is 22 mg/kg body weight (35, 36). Based upon normal growth between 3 and 8 y of age, the expected monthly increase in daily creatinine production would be 3.8 mg.

† At time of end-analysis.

‡ Y, yes; N, no.

§ Different from "low carnitine" mean at $p = 0.036$.

The intent of carnitine replacement therapy in Fanconi syndrome is to restore muscle carnitine levels to normal. This has been difficult to accomplish, despite rapid normalization of plasma carnitine levels. Four of six cystinosis patients failed to exhibit any increase in muscle carnitine levels after up to 18 mo of supplementation (7). Whether due to poor compliance in these patients or some other reason, this finding has tempered enthusiasm for treating cystinosis patients with oral L-carnitine and has raised the issue of why the muscle is so refractory to repletion.

Skeletal muscle uptake of carnitine has been studied in human myotubes in culture (32–34). The process has been shown to have two active transport components, one with high affinity (Km = 2–5 μM) and one with low affinity (Km = 14–160 μM) (33, 34). Although the plasma carnitine concentration in treated patients is within the range of the Km for transport in isolated cells, other factors, such as accessibility to blood supply or competition for transport, may come into play *in vivo*. Thus, very long-term therapy might be required to replete the huge muscle carnitine compartment.

In fact, approximately 5 y of L-carnitine replacement successfully accomplished this feat (Table 1), even in the face of large ongoing renal losses of carnitine (Fig. 2). By maintaining plasma free and total carnitine in the normal range (Fig. 1), one 4-y-old child (patient 6) restored his muscle carnitine to normal by age 11, and five others had normal muscle carnitine levels at 5 to 7 y of age (Table 1). We did not determine whether these five had muscle carnitine deficiency at the start of therapy because it was clear that they would develop muscle carnitine deficiency by 5 to 7 y of age if not supplemented (7). All six initially had plasma carnitine deficiency, and all previously biopsied 5- to 7-y-old cystinosis patients, without carnitine replacement, have exhibited muscle carnitine deficiency (Table 1).

How can the beneficial effects of carnitine therapy be gauged in young children with cystinosis? Objective measures of well-being such as activity level, muscle strength, and endurance are poorly tested in this age group. Growth in height and weight are affected by a vast number of variables and are insensitive outcome parameters, especially in individuals with a chronic disease affecting growth. Similarly, our study showed no correlation between the number of lipid droplets on oil-red-O staining and the improved muscle carnitine status of the children, suggesting that this histologic technique is not sufficiently quantifiable or that other reasons exist for lipid accumulation in the muscles of these patients.

On the other hand, several findings support the possible efficacy of carnitine replacement in children with cystinosis. First, plasma carnitine levels were rapidly and consistently normalized (Fig. 1). Second, plasma FFA have previously been demonstrated to fall with carnitine therapy (7). Finally, normalization of muscle carnitine levels was associated with a rise in creatinine production, which correlates well with lean body mass in adults ($r = 0.88$) (35) and children (36). This encouraging finding must be balanced, however, by recognition that our observations were retrospective, involved a small number of patients, and revealed a relatively small difference between carnitine-replete and carnitine-deficient patients. Furthermore, the normal value for the rate of increase in daily creatinine production has not been experimentally determined, so the clinical significance of this parameter is speculative. One child with a plasma free carnitine concentration of 12 μM had robust creatinine production (Table 2).

What dosage of L-carnitine should be used for carnitine-deficient children with cystinosis? Several studies have demonstrated that gastrointestinal absorption of L-carnitine is slow and incomplete in humans (37–39). Extremely high dosages can be

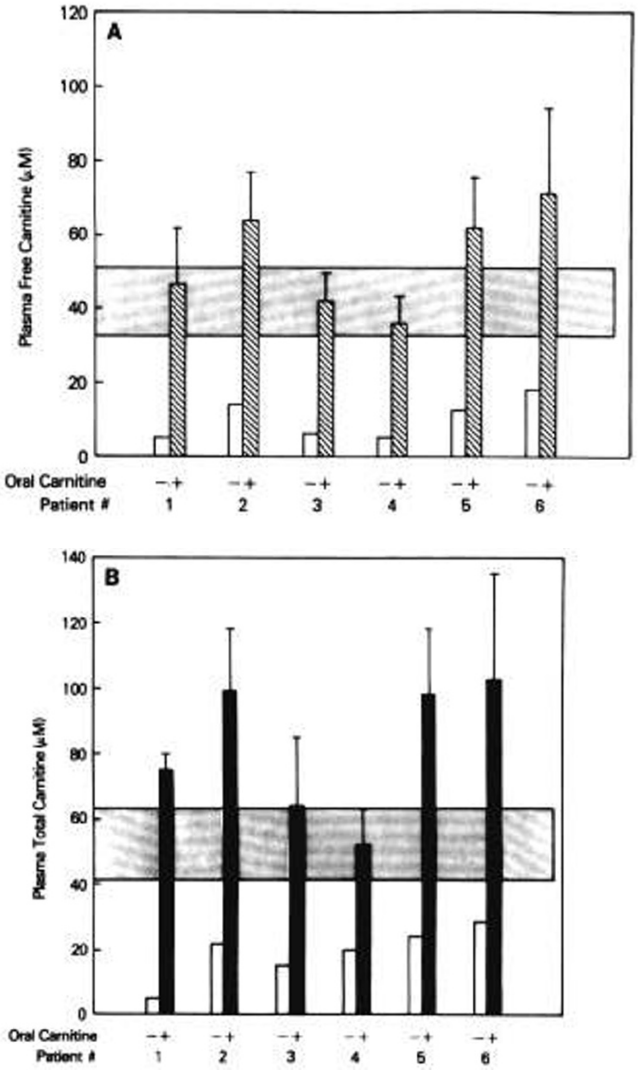

Fig. 1. Plasma carnitine concentrations before (−) and after (+) long-term L-carnitine replacement in six cystinosis children. *A*, Free carnitine; *B*, total carnitine. Values during carnitine replacement are means of between 10 and 19 determinations over 54 to 79 mo. *Bars* show SD. The normal mean ± 1 SD is depicted by the *shaded rectangle.*

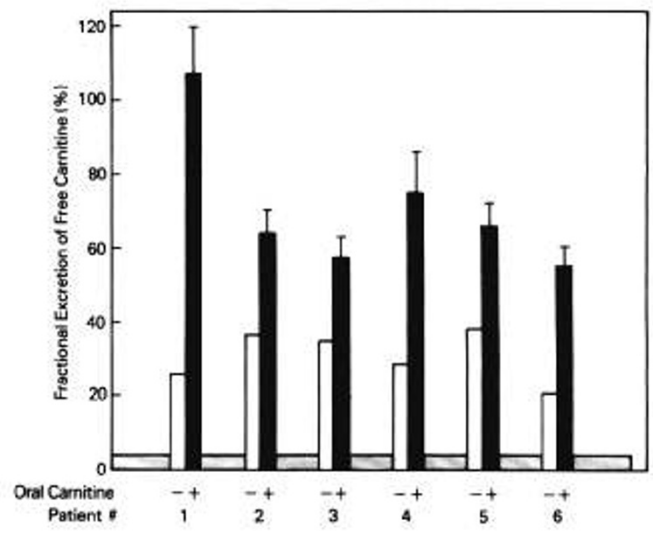

Fig. 2. Fractional excretion of free carnitine before (−) and after (+) L-carnitine replacement in six cystinosis children. *Error bars* show SEM; *shaded area* is the normal range for fractional excretion of free carnitine.

associated with side effects such as diarrhea, nausea and vomiting, and a fishy body odor (40). Our patients maintained normal or elevated plasma free and total carnitine levels when given 78 to 111 mg/kg/d even in the face of substantial urinary carnitine wasting (Fig. 2). Therefore, we recommend a starting dosage of 50 to 100 mg/kg/d, titrated to maintain plasma carnitine levels in the normal range without side effects. Although giving the daily dose divided every 6 h resulted in excellent muscle repletion, oral L-carnitine might prove equally effective when given less frequently.

Before L-carnitine therapy for renal Fanconi syndrome, most cystinosis patients had plasma carnitine deficiency, and none had a normal muscle carnitine content (5, 7). However, all six children with cystinosis who were treated for 5 y with oral L-carnitine had normal muscle carnitine levels. Carnitine replacement in this population will become an increasingly important issue as patients retain their native kidneys for longer periods of time by virtue of therapy with the cystine-depleting agent, cysteamine (12, 13). Unfortunately, this drug does not restore tubular function (9, 12), so the native kidneys of cysteamine-treated cystinosis patients continue to spill carnitine. As a result cysteamine therapy potentially prolongs the duration of muscle carnitine deficiency in pretransplant patients. The ultimate clinical benefits of early carnitine therapy must still be determined; this will require a controlled study involving a large group of patients who are old enough to be tested objectively for muscle strength and activity.

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