Ethylmalonic/Adipic Aciduria: Effects of Oral Medium-Chain Triglycerides, Carnitine, and Glycine on Urinary Excretion of Organic Acids, Acylcarnitines, and Acylglycines

PIERO RINALDO, ROY D. WELCH, STEPHEN F. PREVIS, EBERHARD SCHMIDT-SOMMERFELD, J. JAY GARGUS, JOHN J. O'SHEA, ARTHUR B. ZINN

Department of Genetics, Yale University, New Haven, Connecticut 06510 [P.R., R.D.W., S.F.P., J.J.O.]; Department of Pediatrics, University of Chicago, Chicago, Illinois 60637 [E.S-S.]; Department of Physiology and Section of Medical Genetics, Emory University, Atlanta, Georgia 30322 [J.J.G.]; and Departments of Pediatrics and Genetics, Case Western Reserve University, Cleveland, Ohio 44106 [A.B.Z.]

ABSTRACT. A 9-y-old girl with ethylmalonic/adipic aciduria was hospitalized to determine the possible therapeutic efficacy of oral carnitine and glycine supplementation. To provoke a mild metabolic stress, her diet was supplemented with 440 mg/kg/d of medium-chain triglycerides. She was treated successively with carnitine (100 mg/kg/d) for 5 d, neither carnitine nor glycine for 2 d, and then glycine (250 mg/kg/d) for 6 d. Consecutive 12-h urine collections were obtained throughout the entire period. The urinary excretion of eight organic acids, four acylglycines, and four acylcarnitines, which accumulate as a result of a metabolic block of five mitochondrial acyl-CoA dehydrogenases, were quantitatively determined by capillary gas chromatography, stable isotope dilution gas chromatography/mass spectrometry, and radioisotopic exchange HPLC, respectively. The excretion of each group of metabolites was calculated as the mean percentage of total output (μmol/24 h) during the four phases of the protocol (organic acids/acylglycines/acylcarnitines = 100.0%): 1) regular diet (3 d); 88.1/10.8/1.1; 2) medium-chain triglyceride supplementation (4); 82.5/15.6/1.9; 3) medium-chain triglycerides plus carnitine (5); 79.2/8.2/12.6; and 4) medium-chain triglycerides plus glycine (6); 81.0/18.7/0.3. Comparison between total and individual excretion of acylglycines and acylcarnitines indicates that oral glycine supplementation enhanced the conjugation and excretion of fatty acyl-CoA intermediates as efficiently as carnitine. We propose that oral glycine supplementation should be considered in the treatment of other inborn errors of metabolism associated with abnormal urinary excretion of acylglycines. (*Pediatr Res* 30: 216–221, 1991)

Abbreviations

AC, acylcarnitines
AG, acylglycines
BC, butyrylcarnitine
BG, butyrylglycine
ETF, electron transfer flavoprotein
ETF-QO, ETF-ubiquinone oxidoreductase
HC, hexanoylcarnitine
HG, hexanoylglycine

IVC, isovalerylcarnitine
IVG, isovalerylglycine
MCT, medium-chain triglyceride
OC, octanoylcarnitine
SG, suberylglycine

ETF and ETF-QO sequentially transfer electrons from several mitochondrial flavin-dependent dehydrogenases to the main mitochondrial respiratory chain (1). An inherited defect of either one of these enzymes causes episodes of hypoglycemia and hypoketotic acidosis in association with three different clinical pictures: severe, neonatal onset with congenital anomalies; severe, neonatal onset without congenital anomalies; and mild, later onset (2).

Both ETF and ETF-QO deficiency result in inhibition of several metabolic pathways (fatty acids, lysine, and branched-chain amino acids) at the respective acyl-CoA dehydrogenase step and induce intermittent urinary excretion of dicarboxylic acids (1, 3–5) and acylconjugates (4–9). Although the pattern of organic acid excretion is highly variable, either glutaric acid or ethylmalonic acid and adipic acid are the major components when a diagnostic profile is detected in a given urine sample. Thus, these diseases have been designated as either glutaric aciduria type II (3) or ethylmalonic/adipic aciduria (6).

Several AG have been identified in urine from patients with different organic acidurias (10). Increased excretion of these AG derives presumably from transacylation of the corresponding acyl-CoA that accumulate in these disorders. In urine from patients with ETF or ETF-QO deficiency, excretion of at least five AG is increased: BG, isobutyrylglycine, IGV, HG, and SG (1, 4–7).

The presence and diagnostic significance of specific AC has been evaluated in a number of inborn errors of metabolism (8). In patients with organic acidurias, a relative carnitine insufficiency may occur, secondary to conversion and urinary excretion of accumulated acyl-CoA moieties as AC (9). An impairment of carnitine uptake by tissues may also contribute to producing secondary carnitine deficiency (9). A specific profile of urinary AC has been described in patients with ETF or ETF-QO deficiency, including BC, isobutyrylcarnitine, IVC, HC, and OC (8).

Patients with several organic acidurias have been treated with large oral doses of carnitine (11, 12). The use of glycine for therapeutic purposes has been limited to investigations of patients with isovaleric acidemia, in whom it was found to be

clinically beneficial (13–17). The relative lack of recent interest in glycine supplementation may reflect the assumption that endogenous glycine biosynthesis is active enough not to require exogenous supplementation, regardless of chronic losses via urinary excretion of pathologic AG.

In this study, we first induced a mild metabolic stress (dietary MCT oil supplementation) in a 9-y-old girl with a proven deficiency of ETF-QO whose urinary organic acid profile was consistent with the biochemical phenotype of ethylmalonic/adipic aciduria (6). We then investigated the effects of either carnitine or glycine oral supplementation on organic acid and acylconjugate excretion in continuous 24-h urine collections over a period of 20 d. The aim of this study was to determine the relative efficacy of oral carnitine *versus* oral glycine supplementation to enhance the removal of intracellular acyl-moieties that accumulate as result of multiple metabolic blocks in fatty acid and amino acid metabolism.

MATERIALS AND METHODS

Case report. The patient reported on here was the first to be diagnosed with ethylmalonic/adipic aciduria (6). Her primary defect is a mild form of ETF-QO deficiency (18% residual activity) (2).

During the last 3 y, she has been in satisfactory condition without any hospitalizations of medical problems. She has been on a low fat (15% of total calories) and low protein (1.1–1.2 g/kg/d, 15% of caloric intake) diet. At the time of the last physical examination (September, 1989), her height and weight were 168.4 cm (75th to 90th percentile) and 57.0 kg (50th to 75th percentile), respectively. No sign of neurologic handicaps and no hepatomegaly were found. Her intelligence quotient was in the normal range.

Clinical research protocol. The protocol was approved by the Yale Human Investigation Committee (HIC no. 1430), and informed parental consent was obtained for administration of MCT oil and oral carnitine and glycine supplementation. At 9 y of age (December 1981), she was admitted to the Yale Children's Clinical Research Center for 22 d. Her height and weight were 133 cm and 31.2 kg, respectively. After 3 d on a hospital diet adjusted to her caloric needs, her diet was supplemented with 440 mg/kg/d of MCT oil (4.6 g three times a day during meals) to provoke a mild metabolic stress. One dose was 1/9 of the amount, used in a previous study (6), that had induced severe vomiting and lethargy 45 min after ingestion. This diet was well tolerated. On d 6, however, a tentative increase of the MCT oil to 575 mg/kg/d (18.0 g) led to the onset of postprandial nausea, vomiting, and abdominal pain after the second administration. The protocol was continued at the lower dosage (total MCT dose on d 6: 16.6 g or 530 mg/kg/d). She promptly recovered and, from that point on, tolerated the MCT oil well.

Beginning on d 8, she was treated with oral carnitine supplementation (100 mg/kg/d in three divided doses) for 5 d (only one dose the 1st day), given 15 min before meals, mixed with orange or apple juice. On d 13, after the end of the carnitine supplementation, she presented the symptoms of a viral infection with mild fever (38°C), general malaise, nausea, and vomiting. To avoid the risk of more severe symptoms, MCT oil was withdrawn from her diet for 2 d. She ate poorly for these 2 d and had inadequate caloric intake. On d 15, after complete clinical recovery, the MCT oil was reintroduced and glycine supplementation was added (250 mg/kg/d in three divided doses), the latter given 30 min before meals. Soon after glycine supplementation was started, the patient appeared to be more energetic and her appetite improved significantly, as did her interest and performance in scholastic duties. None of these changes were noted during the period of carnitine supplementation. On the day after the conclusion of the protocol, however, the patient suffered the same symptoms described above but in a more severe form.

After 1 d of observation, she recovered and was discharged in good condition.

With the exception of d 13–14, her dietary intake was relatively consistent. Her caloric intake during d 3–12 and 15–20 was 60 ± 14 kcal/kg/d, with protein, fat, and carbohydrate representing the source of 8.7 ± 2, 23.6 ± 4, and 67.6 ± 4.9% of total calories, respectively.

After the conclusion of this clinical investigation protocol, the patient was started on chronic glycine therapy (150 mg/kg/d), which was discontinued approximately 2 y later. During this period, she suffered few or no medical problems, and distinct improvements in her school performance and social interaction were observed. The reported reason for discontinuing glycine supplementation was the patient's refusal to comply with any restrictions or therapeutic measures.

Organic acid analysis. For organic acid and acylconjugate determination, 40 consecutive 12-h urine collections were pooled at 4°C until the end of each period and stored at −20°C. Quantitative determinations were performed by capillary gas chromatography using pentadecanoic acid (100 μg) as internal standard (18). Results are expressed as μmol/24 h.

Carnitine and AC analysis. Free carnitine and individual C_2–C_4 carnitine esters were quantitated as described earlier (19), except that extraction and purification of the urine before radioisotopic exchange were omitted. Complete exchange of radiolabeled carnitine into short-chain AC (C_2–C_4) was verified after adding various concentrations of authentic standards to the reaction mixtures. In two of the urine samples collected during carnitine supplementation, isobutyrylcarnitine and BC were separated by HPLC using a different solvent system (20). Two C_5-AC were also detected after incubation at 37°C for 4 h. One of them coeluted with the pure standard of IVC. The other had a longer retention time. No attempt was made to characterize further or quantitate these compounds. For the quantitation of HC and OC, a known amount of decanoylcarnitine was added as internal standard (21).

AG analysis. HG and SG were analyzed by stable isotope dilution analysis as previously described (7, 22). Butyryl[1,2-^{13}C] glycine was synthesized from butyrylchloride and [1,2-^{13}C]glycine. [4,4,4-D_3]IVG was already available from a previous study (23). To quantitate BG and IVG, the initial temperature of the gas chromatography method was 130°C.

Amino acid analysis. Glycine determination was performed using a Beckman 7300 amino acid analyzer equipped with a lithium 10-cm column (24).

RESULTS

Organic acid excretion. Figure 1*A–D* shows the profiles of urinary organic acids in four samples corresponding to the urine collections of d 6, 12, 17, and 21 (acute episode a day after the termination of the protocol), respectively. The peaks marked *1* to *8* correspond to the eight metabolites (ethylmalonic acid, methylsuccinic acid, and C_5–C_{10} dicarboxylic acids) quantitated to express, for the purpose of this study, the total organic acid excretion (μmol/24 h). The excretion of glutaric acid, adipic acid, suberic acid, and sebacic acid was smaller on those days that the patient was receiving supplementary glycine (Fig. 1*B*) or carnitine (Fig. 1*C*) than on those days when she was not (Fig. 1*A*). In contrast, the organic acid profile during an acute episode (Fig. 1*D*) was similar to a typical profile of glutaric aciduria type II.

The pattern of urinary organic acid excretion during the four phases of the clinical trial (Fig. 2*A*) is shown in Figure 2*B–D*. The total organic acid excretion is shown in figure 2*B*. In Figure 2*C*, the total organic acid excretion was subdivided into three groups, expressed as the respective percentage in each day: *1*) ethylmalonic acid plus methylsuccinic acid; *2*) glutaric acid; and *3*) C_6–C_{10} saturated and monounsaturated dicarboxylic acids. The peaks of excretion observed on d 6, 13–14, and 20 (Fig. 2*B*) correlated with the severity of the clinical symptoms. The glutaric
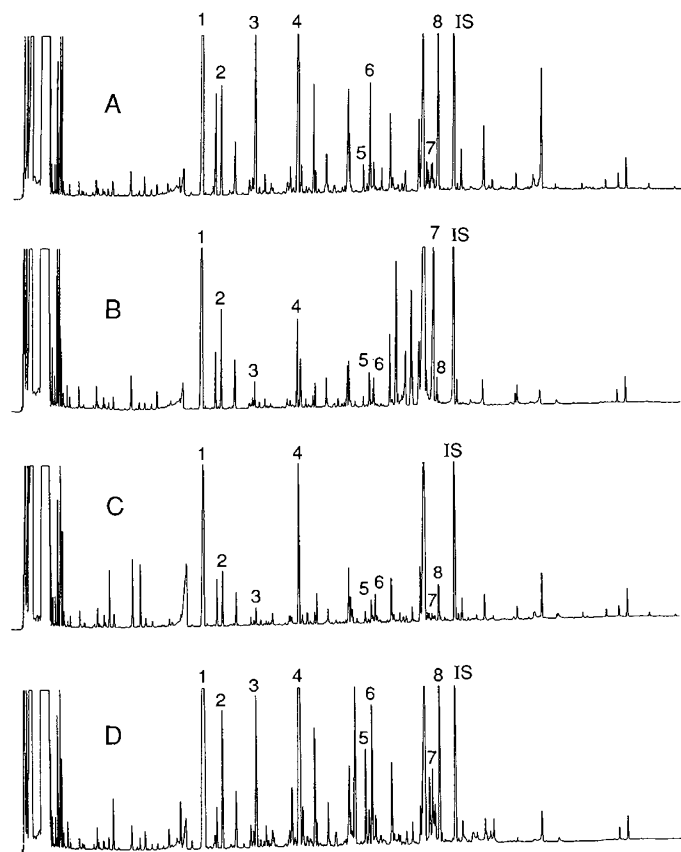
Fig. 1. Organic acid profiles of patient urines. Capillary gas chromatographic profiles of organic acid trimethylsilyl derivatives in four urine samples corresponding to the 0800- to 2000-h urine collections of *A*, d 6 (MCT 530 mg/kg/d, mild postprandial symptoms); *B*, d 12 (MCT 440 mg/kg/d + carnitine 100 mg/kg/d, clinically well); *C*, d 17 (MCT 440 mg/kg/d + glycine 250 mg/kg/d, clinically well; and *D*, d 21 (acute episode after the termination of the protocol). Peak legends: *1*, ethylmalonic acid; *2*, methylsuccinic acid; *3*, glutaric acid; *4*, adipic acid; *5*, octenedioic acid (three peaks); *6*, suberic acid; *7*, decenedioic acid (three peaks); *8*, sebacic acid; and IS, internal standard (pentadecanoic acid). All peak identifications were confirmed by gas chromatography.

acid excretion was found to be a specific marker of metabolic decompensation, ranging between 0.2 and 2% of the total organic acid excretion when the patient was clinically well, and up to 22% during symptomatic episodes.

AC excretion. The AC excretion pattern is shown in Figures 2*D* and 3. C_4-AC were the major carnitine esters excreted during carnitine supplementation. The total excretion of free carnitine and its esters was subject to marked changes on a day-to-day basis. The average ratio among the $C_4/C_6/C_8$ AC, however, was 85/5/10 (%), with only minor fluctuations during the different phases of the protocol. The average urinary excretion of the AC esters derived from fatty acid oxidation was somewhat increased during MCT feeding as compared with the period of standard diet (Fig. 2*D*, Table 1), whereas the excretion of free carnitine remained unchanged.

Carnitine supplementation had no significant effect on carnitine ester excretion during the first 36 h of supplementation, but was followed by a progressive increase of free carnitine and AC excretion, which reached its peak on the 5th and last day of carnitine supplementation. At that time, the AC fraction accounted for 19% of the total metabolite excretion. Under glycine supplementation, AC excretion decreased to less than baseline levels (BC + HC + OC: <2.0 μmol/12 h, or <7.0 μmol/g creatinine).

AG excretion. The AG excretion pattern is shown in Figure 2*D*. HG was the prominent AG in urine, with an average ratio
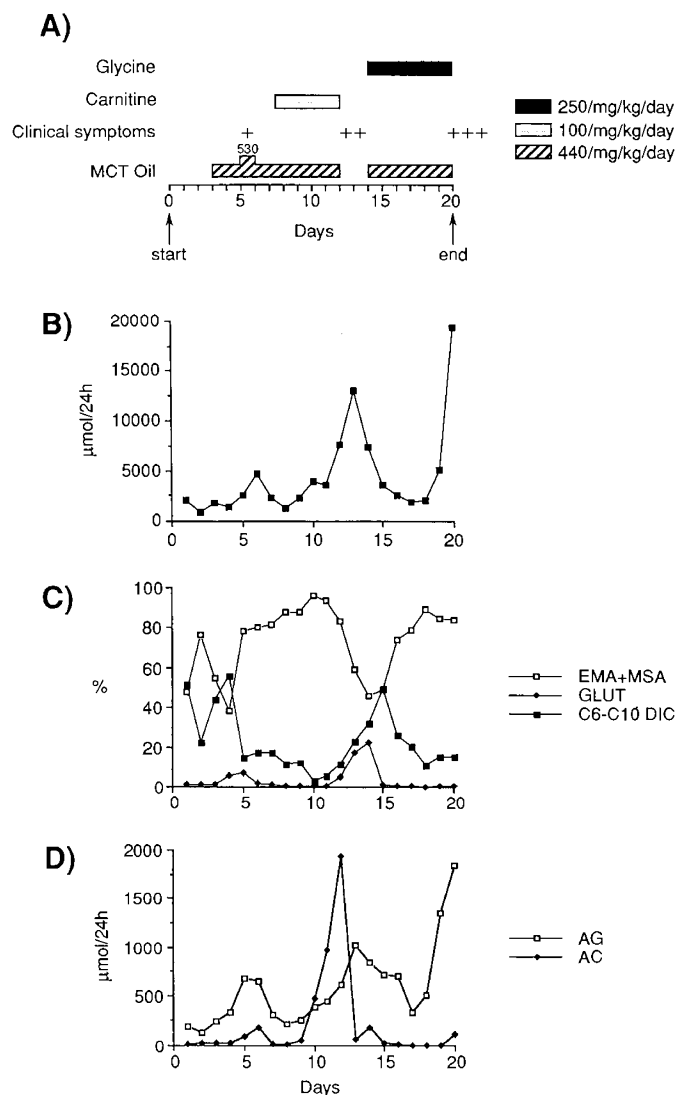

Fig. 2. Time course of organic acid, AG, and AC excretion. *A*, Periods of MCT oil, carnitine, and glycine oral supplementation during the protocol of clinical investigation. Clinical symptoms (for further details, see text): +, mild; + +, moderate; and + + +, severe. *B*, Time course of organic acid excretion (sum of metabolites 1 to 8 as listed in the legend to Fig. 1). Values expressed as μmol/24 h. *C*, Time course of ethylmalonic acid plus methylsuccinic acid (*EMA + MSA*), glutaric acid (*GLUT*), and C_6-C_{10} saturated and monounsaturated dicarboxylic acid (*C6-C10*) excretion. Values expressed as percentage of the total organic acid excretion. *D*, Time course of AC and AG excretion. Values are expressed as μmol/24 h.

among the $C_4/C_5/C_6/C_8$ AG of 6/11/50/33 (%) when the patient was on a standard diet, 15/13/40/32 during MCT oil supplementation, and 26/11/40/23 when the patient was receiving MCT + carnitine, respectively (Table 1). In contrast to the excretion of the other AG, BG excretion increased during carnitine supplementation, in parallel with the pattern of AC excretion. When glycine was given, the relative excretion of BG further increased with parallel decreases in the proportions of C_5 and C_6. The average AG ratio during this period was 30/10/32/28, as determined by analysis of 12 consecutive 12-h urine collections.

For the purpose of comparison with available normal controls, AG excretion was also calculated as mmol/mol of creatinine. BG (2.4–234.9) and HG (9.8–168.2) excretion were always above the range of control values: 0.02–1.6 and 0.13–1.2 (8), respectively. IVG and SG excretion were found within the range of controls (0.21–10.2 and <0.005–5.4) in 63 and 58%, respectively, of the urine samples.
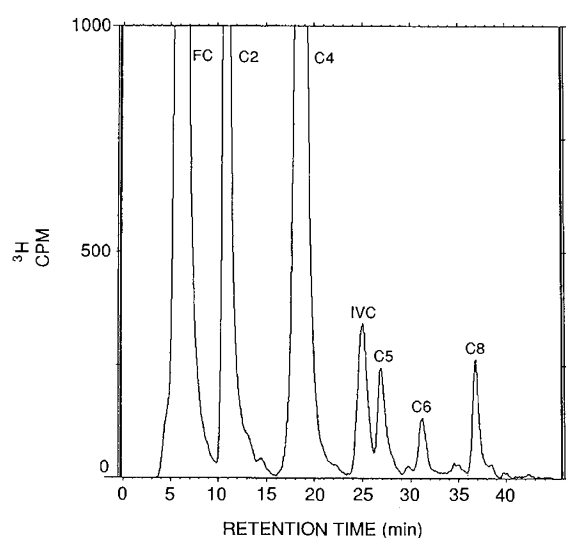
Fig. 3. HPLC chromatogram of urinary carnitine esters. Profile of urinary carnitine esters in the sample corresponding to the 0800- to 2000-h urine collection of d 14. Peak legends: FC, free carnitine; C_2, acetylcarnitine; C_4, BC (90%) plus isobutyrylcarnitine (10%); IVC, presumed IVC; C_5, "other" C_5 AC; C_6, HC; and, C_8, OC.

After initiation of glycine supplementation, increased AG excretion was not evident for approximately 24 h. It then increased progressively, reaching a maximum of 28% of total metabolite excretion. Despite a 10-fold increase of free glycine excretion compared with the period of standard diet, the ratio of urinary AG/glycine excretion remained unchanged (Table 1).

Because of the unfortunate loss of plasma samples collected during this protocol, plasma glycine values are not available. In a sample collected 6 mo later, glycine concentration was 428.5 μmol/L (controls: 117–283 μmol/L). At that time, the patient was receiving glycine 300 mg/kg/d.

Comparison among organic acids, AC, and AG excretion. Table 1 shows the range and median values (in μmol/24 h) of organic acids, free carnitine, free glycine, and individual AC and AG excretion during each phase of the protocol. In terms of the absolute amounts of acylconjugates excreted, the results observed with carnitine and glycine supplementation were comparable.

On the last days of supplementation, d 12 and 20, respectively, approximately 2 mmol/24 h of AC and AG were excreted (Fig. 2D). Because a steady state was not reached for acylconjugate excretion with either carnitine or glycine supplementation, no statement can be made about the "maximal" excretion associated with oral carnitine or glycine supplementation in this patient.

Figure 4 shows the comparison (expressed as the percentage of total metabolites) among organic acid, AG, and AC excretion during the four phases of the protocol. Before any supplementation was started, AG excretion accounted for 10% of total urinary organic acids and acylconjugates and was 10-fold higher than AC output. As expected, the addition of MCT oil in the diet increased the total excretion of dicarboxylic acids and acylconjugates. However, the relative proportion of dicarboxylic acids, AC, and AG remained relatively constant.

To assess further the competition between the two alternative conjugation pathways, the BG/BC and HG/HC ratios during the entire length of the protocol are presented in Figure 5. The time course of these ratios provides a detailed picture of the role of the two alternative pathways for conjugation of butyryl-CoA and hexanoyl-CoA at any given day of the protocol.

DISCUSSION

Ethylmalonic/adipic aciduria was considered an appropriate disease model to assess the biochemical effects of both glycine and carnitine supplementation because the disease *1*) has an intermittent course with prolonged periods of clinical stability; *2*) is characterized by a typical organic acid profile; and *3*) is associated with pathologic excretion of several AG and AC. We have shown that both oral carnitine and glycine supplementation diverted the disposal of excess acyl-moieties from the ω-oxidation pathway to the synthesis of acylconjugates. Careful quantitative analysis of acyl-group excretion suggests that glycine supplementation may provide a means of treating patients with ETF-QO deficiency that is as efficient as carnitine supplementation. Under a standard diet and during MCT oil supplementation, the detoxification response of this patient was predominantly mediated by glycine rather than carnitine-conjugation of excess mitochondrial acyl-CoA. In relative terms, the AG fraction was 10- to 20-fold higher than AC excretion under both a basal diet and MCT oil supplementation and up to 200-fold higher during glycine sup-

Table 1. *Urinary excretion of organic acids, carnitine, glycine, and acylconjugates**

	Standard diet	MCT	MCT and carnitine	MCT and glycine	Controls
Organic acids	870–1988 (1819)	1452–4702 (2423)	1271–7664 (3599)	1886–19342 (3076)	NA
Free carnitine	8–49 (13)	8–55 (24)	190–2648 (794)	4–33 (6)	35–127†
AC					
AcC	5–21 (11)	24–226 (113)	19–884 (169)	6–28 (9)	9–24
C_4 fraction‡	6–18 (17)	12–153 (47)	37–1751 (630)	3.0–89 (5)	4–6
HC	0.5–0.7 (0.5)	0.4–9 (1)	1–76 (31)	0.6–7 (1)	ND
OC	1–2 (1)	1–19 (13)	2–107 (58)	0.4–14 (1)	ND
Free glycine	493–1122 (596)	1147–1460 (1375)	1602–2155 (1955)	4482–9048 (6668)	116–1606
AG					
BG	8–13 (12)	22–103 (83)	62–139 (103)	114–735 (212)	NA
IVG	17–26 (19)	32–118 (63)	20–57 (45)	49–122 (75)	NA
HG	60–119 (94)	110–248 (203)	81–248 (148)	113–477 (233)	NA
SG	37–84 (66)	93–224 (154)	53–212 (78)	58–512 (203)	NA
Ratios§					
AC/free carnitine	0.4–1.5 (1)	0.4–7.7 (2)	0.3–2.9 (0.7)	0.9–1.7 (1)	NA
AG/free glycine	0.2–0.4 (0.2)	0.2–0.5 (0.3)	0.1–0.3 (0.2)	0.1–0.4 (0.2)	NA
AG/AC	6–25 (9)	4–24 (12)	0.3–5 (0.7)	17–255 (74)	NA

* Range and median of values are expressed as μmol/24 h. ND, not detectable; NA, not available (see text); AcC, acetylcarnitine.

† $n = 3$, age 5–8 y.

‡ Ninety percent BC, 10% isobutyrylcarnitine.

§ AG and AC fractions include the metabolites shown above with the exclusion of AcC. AcC was not included in the total AC excretion because its excretion is not directly dependent on the activity of any enzyme primarily affected by the ETF-QO defect.
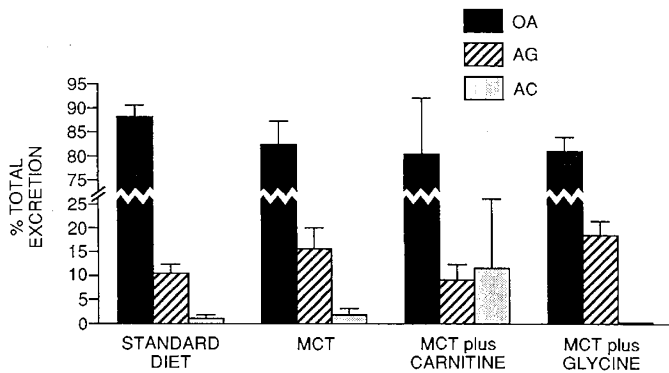
Fig. 4. Relative contributions (%) or organic acids, AG, and AC to the total metabolite excretion during the four phases of the protocol. The contributions of organic acids (*OA*), AG, and AC fractions are shown as mean value and SD (*vertical bar*) of the total metabolite excretion (μmol/24 h) in each of the four phases of the protocol.

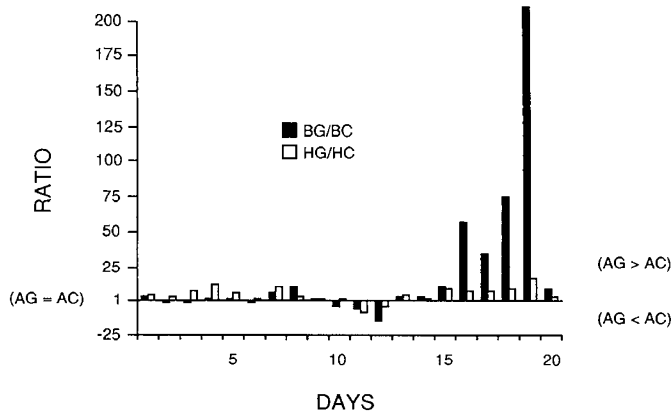Fig. 5. Time course of BG/BC and HG/HC ratios. *Upward bars* indicate that the amount of BG and HG was in excess of the respective carnitine ester excretion (μmol/24 h) in a given day (*AG > AC*). *Downward bars* indicate the opposite situation (*AG < AC*). BC values were calculated as 90% of each C_4-AC fraction.

plementation, whereas the median AC excretion was less than twice the median AG excretion during the period of carnitine supplementation (Fig. 3). The urinary AG/free glycine ratio remained constant throughout the protocol (Table 1), indicating a mass action effect for glycine conjugation. In absolute terms, the excretion of AC and AG were comparable on the last days of oral carnitine and glycine supplement.

We observed that free glycine excretion rose after MCT oil was introduced into the diet. Hyperglycinemia/hyperglycinuria had been documented in our patient during earlier episodes of hypoglycemia and acidosis (25). Although we cannot provide an explanation for this reaction to acute episodes and to MCT oil supplementation, it may be related to the accumulation of intracellular acyl-CoA. Although glycine is potentially neurotoxic, patients with ethylmalonic/adipic aciduria (or other inborn errors) are unlikely to reach, after oral glycine supplementation, plasma and cerebrospinal fluid glycine concentrations of the order of magnitude found in nonketotic hyperglycinemia (26).

Until now, the clinical use of glycine supplementation has been limited to patients with isovaleric acidemia (13–17, 27, 28). Oral glycine supplementation was well tolerated by all of the patients with isovaleric acidemia except one case reported by De Sousa *et al.* (28), who had onset of encephalopathic features soon after the start of glycine supplementation (300 mg/kg/d). In our patient, the same dose induced no symptoms and only a moderate elevation of plasma glycine concentration. Naglak *et al.* (17) did not observe any side effects in two patients treated with glycine supplementation of 600 mg/kg/d. Similarly, no side

effects have been reported with the use of larger amounts of glycine (825 mg/kg/6 h) in oral rehydration solutions used for infantile diarrhea in children 5 y of age or younger (29). For these reasons, the adverse reaction described by de Sousa *et al.* should be seen as the exception rather than the rule. Nevertheless, given the still limited experience with oral glycine supplementation in patients with inborn errors of metabolism, we recommend monitoring plasma glycine levels in patients receiving oral glycine supplementation.

Carnitine has been used widely for the treatment of several organic aciduria, with most of the emphasis placed on disorders of propionate metabolism (9) and fatty acid β-oxidation (8). However, there is no firm evidence that carnitine supplementation is truly beneficial for patients with individual or multiple acyl-CoA dehydrogenase deficiencies (12). A positive link between enhancement of acylcarnitine excretion and clinical improvement after carnitine therapy sometimes has been assumed rather than documented in patients with secondary carnitine deficiency. In one of the few specific clinical investigation protocols published on this matter, Treem *et al.* (30) studied a patient with medium-chain acyl-CoA dehydrogenase deficiency and found no improvement in the patient's fasting tolerance after 3 mo of carnitine supplementation.

The combined therapeutic effect of carnitine and glycine supplementation has received little attention. Roe and his associates investigated a 6-mo-old infant with propionic acidemia (31) and a 4-y-old boy with isovaleric acidemia (27). In the first study, a higher threshold of protein tolerance was achieved when the patient was supplemented at the same time with carnitine (100 mg/kg/d) and glycine (150 mg/kg/d). In the second patient, the excretion of IVG and IVC was determined in response to loading tests with leucine (25 and 50 mg/kg), leucine plus glycine (150 mg/kg) and leucine plus carnitine (322 mg/kg). When given at the higher dosage without carnitine or glycine, leucine induced nausea and vomiting, but did not do so with concomitant administration of either carnitine or glycine.

Thus, there remains the need to investigate further the potential benefit of glycine in disorders previously found responsive, at least biochemically, to glycine or carnitine supplementation. We propose that glycine supplementation, possibly in combination with carnitine supplementation, should be considered in the treatment of other inborn errors of metabolism distinguished by urinary excretion of pathologic AG.

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