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The response to L-carnitine and glycine therapy in isovaleric acidaemia

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Abstract. The profound metabolic disturbances which occur in isovaleric acidaemia are due to the intramitochondrial accumulation of isovaleryl coenzyme A (CoA) with a consequent reduction in the availability of free CoA. Secondary carnitine insufficiency is also a feature of this and other disorders of organic acid metabolism. A patient who presented at 2.5 years of age was diagnosed using capillary GC-MS as having isovaleric acidaemia. She showed the full spectrum of abnormal organic acids previously associated with the 'neonatal' form of the disease despite her late presentation, indicating that it is inappropriate to refer to acute early and late onset forms of isovaleric acidaemia. Instead, a spectrum of disease exists, determined by environmental factors, residual enzyme activities and modifying effects of different phenotypes in different individuals. She also showed evidence of carnitine insufficiency. An oral challenge with L-carnitine resulted in the excretion of large amounts of urinary acylcarnitines which were shown by use of fast atom bombardment mass spectrometry to be primarily isovalerylcarnitine. Regular glycine supplementation caused no significant increase in urinary isovalerylglycine and had to be stopped because of side-effects after 5 days. An oral L-carnitine challenge during glycine supplementation resulted in a marked increase in isovalerylglycine excretion, again associated with the excretion of large amounts of isovalerylcarnitine. Carnitine acts by removing (detoxifying) intramitochondrial isovaleryl groups and, in the presence of glycine, it promotes the formation of isovalerylglycine. We believe L-carnitine supplementation is of value in the treatment of isovaleric acidaemia and that, in the present case, L-carnitine together with a moderate dietary restriction has proved to be the optimum form of therapy.

Key words: Isovaleric acidaemia – Carnitine – Isovalerylcarnitine – Glycine therapy – Carnitine therapy

Introduction

Isovaleric acidaemia is a disorder of leucine catabolism characterised clinically by episodes of acidosis and coma, an objectionable body odour and mild psychomotor retardation [3, 17]. Biochemically this disorder is caused by a deficiency of isovaleryl coenzyme A (CoA) dehydrogenase and there is a consequent intramitochondrial accumulation of isovaleryl CoA and its metabolites. A group of patients have also been described who present with a fulminant and often lethal illness during the first few weeks of life [13, 16]. Overwhelming sepsis and pancytopaenia contribute to the high mortality in this group [11]. If they survive the neonatal period with appropriate treatment their subsequent course is that of the intermittent form of the disease.

Isovaleric acid is invariably present in the body fluids of patients in greatly increased amounts, and 3-hydroxyisovaleric acid [18] and isovalerylglycine [1] have also been identified. Some patients excrete a number of additional urinary metabolites [19] such as methylsuccinic acid, 4-hydroxyisovaleric acid, methylfumaric acid, isovalerylglutamic acid, 3-hydroxyisoheptanoic acid and isovalerylglucuronide. These latter compounds have been described as being typical of the severe neonatal form of isovaleric acidaemia and their presence has been taken as evidence for biochemical as well as clinical heterogeneity in this disorder.

Glycine therapy has been advocated for the regular treatment of patients with isovaleric acidaemia [20] and for the management of acute ketoacidotic episodes [12]. We have shown previously that patients with this and related disorders have an insufficiency of L-carnitine [6, 7] and have proposed supplemental L-carnitine in their treatment [14]. This paper describes studies on the role of L-carnitine with and without dietary and glycine therapy in a patient with isovaleric acidaemia.

Clinical description

A 2.5-year-old girl was admitted to hospital with a short history of vomiting and became rapidly unwell with lethargy and irritability. She had been born by a normal delivery at term to non-consanguineous parents. An older female sibling was well and there was no maternal history of spontaneous abortions or neonatal deaths. Birth weight was 3.6 kg and she remained well until 12 days of age. She was breast-fed for 3 days and given an infant formula feed thereafter. From 12–17 days she was hospitalised because of poor feeding and constipation. During this admission she was noted to be hypotonic and jittery and to have an abnormal high-pitched cry. No biochemical investigations were done. She was diagnosed as having chickenpox at 6 months and measles at 1 year, both of which followed a mild course.

At 17 months she was referred to the paediatric department of her hospital because of delayed development and was found to have a mild spastic diplegia. Investigations at this

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Abbreviations: CoA = Coenzyme A; TMS = trimethylsilyl; S.D. = standard deviation; DEAE = diethylaminoethyl; FAB = fast atom bombardment

time revealed normal plasma amino acids, no serological evidence of congenital infection, a normal skull X-ray and a normal EEG. Her handicap was not severe and she progressed well. At 2 years she was admitted to hospital with a history of diarrhoea followed by persistent vomiting. She became dehydrated and acidotic and improved only after intravenous rehydration.

A few days prior to her admission at 2.5 years she had had a mild upper respiratory tract infection. Immediately prior to this she had consumed what were for her large quantities of eggs and fishcakes, although her diet had previously been that of a normal infant. Following admission she rapidly became dehydrated with stertorous respirations, and a "cheesy" smell was noted on her breath. She was found to have a marked metabolic acidosis (arterial blood pH 7.22 and the base deficit −18.7 meq/l). Blood urea was 14.8 mmol/l, blood glucose was 2.9 mmol/l and calcium 1.64 mmol/l. Her other plasma electrolytes were normal as were her haemoglobin and white cell count. She was treated with intravenous fluids and sodium bicarbonate and her condition improved over the next 48 h. Examination of her urine for organic acids by gas chromatography and mass spectroscopy allowed the diagnosis of isovaleric acidaemia to be made.

One month later she was admitted for metabolic studies to the Clinical Research Centre whilst clinically well. She was an alert and well-nourished child. Her weight was on the 50th centile for her age and her height was on the 90th centile. She had a mild spastic diplegia. She had global developmental delay with in particular slow acquisition of language and fine motor skills. Developmental assessment showed her to be delayed in most areas of development (Griffiths Mental Developmental Scale, overall quotient = 81). Physical examination gave otherwise normal results.

Methods

Organic acids were quantitatively extracted from urine and plasma ultrafiltrate using DEAE-Sephadex by established procedures [5] and analysed by capillary gas chromatography of their trimethylsilyl (TMS) and TMS-ethoxime derivatives on 25 m fused silica columns coated with a non-polar chemically bonded polymethyl-siloxane (CP-SIL-5, Chrompak UK, London). A split injection (70:1) of a 2 µl sample at 200°C was temperature programmed at 6°C min^{-1} from 70°–250°C. The carrier gas was Helium, 1.4 ml/min^{-1}. Components were identified using retention indices and quantified using n-tetracosane as a standard. Identification was subsequently confirmed using capillary gas chromatography/mass spectrometry on a Varian MAT 112 mass spectrometer. Plasma amino acids were measured by ion exchange methods on an LKB analyser.

Free carnitine was measured by a radioenzymatic assay using a modification of existing methods [4]. The sample of plasma or urine to be analysed was incubated directly with [1^{-14}C] Acetyl-Coenzyme A (Amersham International, England) in the presence of a Hepes buffer and N-ethylmaleimide as a trap for free Coenzyme A, and carnitine acetyltransferase (Sigma, St. Louis, USA) was added. Total carnitine (free plus acylcarnitines) was measured by first hydrolysing a sample of plasma or urine with KOH and then neutralising with HCl before the above steps. Following incubation the reaction mixtures was passed down an anion exchange resin column of Dowex 2-X8 (200–400 mesh in chloride form) (Biorad Laboratories, Calif., USA). The isotope content of the effluent was determined using a liquid scintillation spectrometer (Phillips PW4700). Calibration was by means of standard solutions of L-carnitine (Sigma) and 0-acetyl-L-carnitine (PL Biochemicals, Wisconsin, USA).

Acylcarnitines were identified in urine after either Dowex 1 purification or Dowex 50 extraction by fast atom bombardment (FAB) mass spectrometry on a Varian MAT 731 mass spectrometer using Xenon gas and a glycerol matrix. High resolution mass measurements were made as required on related ions.

Results

Urinary and plasma organic acids and amino acids

Analysis of urine and plasma obtained during the acute acidotic episode at 2.5 years for organic acids revealed the presence of a number of components in greatly increased amounts (Fig. 1a, 1b). Isovalerylglycine, 3-hydroxyisovalerate and 4-hydroxyisovalerate were present in urine and plasma and in addition methylsuccinate, methylfumarate (mesaconate), isovalerylglutamate and isovalerylglucuronide were observed in urine (Fig. 1a; Table 1). Analysis of urine and plasma amino acids was normal except for high glycine concentrations, 586 µmol/l in plasma and 684 mmol/mol of creatinine in urine (normal levels at this age are 200 (± 53) µmol/l in plasma and 113–486 mmol/mol creatinine in urine).

At the time of her admission to hospital for further investigation the patient was on an unrestricted diet with a protein intake of between 2.25 and 3 g/kg body weight per day, equivalent to a leucine intake of approximately 210–280 mg/kg per day. She was observed in hospital for 3 days during which time baseline data were collected. At this time, when she was clinically well, her urinary organic acid excretion (as measured in eight samples over a period of 3 days) was normal except for the presence of large amounts of isovalerylglycine (Table 1). The urinary excretions of the other abnormal metabolites identified during her acute episode were not significantly elevated in these specimens. Plasma and urinary amino acids, including glycine, were normal.

Carnitine measurements and the response to carnitine

During her acute acidotic episode at 2.5 years of age total plasma carnitine was very low and most of this was in the form of acylcarnitines, with an abnormally high acylcarnitine: total carnitine ratio (Table 1). She excreted large amounts of acylcarnitines and her urinary acylcarnitine: free carnitine ratio was high. Immediately before the present study when the patient was clinically well she had low plasma carnitine levels but normal urinary carnitine excretion (Table 1).

L-Carnitine, 200 mg/kg body weight (2.65 g), was administered orally as a single dose. Consecutive urine specimens were collected for 24 h and analysed for carnitine and organic acids. Plasma carnitines and organic acids were also analysed over this period. The results for carnitine are shown in Fig. 2A with urinary excretion expresed in µmol/h. Urinary carnitine excretion rose within 2 h of administration of carnitine to a maximum concentration of 1382 mmol/mol creatinine. The rise in the excretion of acylcarnitines was relatively greater than that of free carnitine. FAB mass spectrometry of acyl-

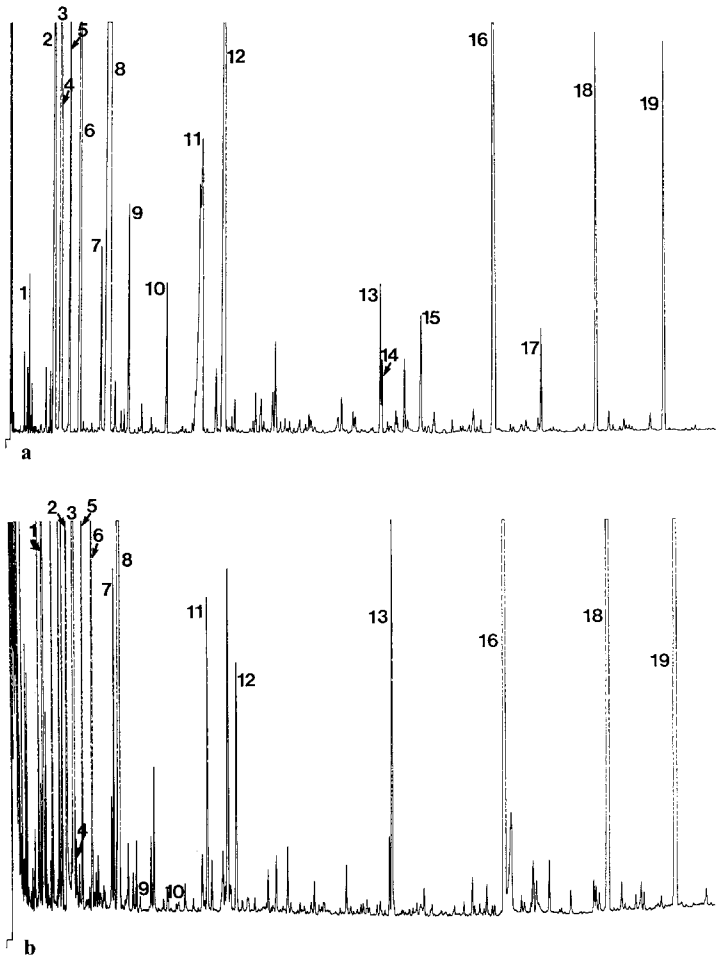

Fig. 1. Chromatograms of urinary (**a**) and plasma (**b**) organic acids at the time of presentation. Peaks are: 1. Lactate; 2. Sulphate; 3. 3-Hydroxybutyrate; 4. Acetoacetate (peak 1); 5. Acetoacetate (peak 2); 6. 3-Hydroxyisovalerate; 7. 4-Hydroxyisovalerate; 8. Phosphate; 9. Methylsuccinate; 10. Methylfumarate; 11. N-Isovalerylglycine-TMS1; 12. N-Isovalerylglycine-TMS2; 13. Citrate; 14. Isocitrate; 15. Isovalerylglutamate; 16. Urate; 17. Isovalerylglucuronide; 18. Tetracosane (internal standard); 19. Hexacosane (internal standard)

Table 1. Plasma and urinary organic acids and carnitines at diagnosis and at time of study

Acid	Urine (mmol/mol creatinine)			Plasma (μmol/l)		
	at diagnosis	CRC admission[b]		at diagnosis	CRC admission	
Lactic	118	24	(11–59)	1892	1610	
3-Hydroxybutyric	2553	29	(13–42)	1579	138	
Acetoacetic	1117	nd[a]		77	28	
3-Hydroxyisovaleric	1611	17	(9–38)	189	8	
4-Hydroxyisovaleric	160	nd		54	3	
Methylsuccinic	183	nd		2	nd	
Methylfumaric (mesaconic)	149	nd		2	nd	
Isovalerylglycine	2716	1980	(1510–2646)	73	nd	
Isovalerylglutamate	109	60	(37–72)	< 1	nd	
Isovalerylglucuronide	49	nd		nd	nd	
Carnitines			Normal (mean ± SD)			Normal (mean ± SD)
Free carnitine	2.2	1.7	12.2 (± 7.6)	2.8	7.9	29.5 (± 4.3)
Acylcarnitines	24.1	8.5	15.1 (± 3.2)	7.7	7.1	4.6 (± 3.4)
Acyl/free ratio	11.0	5.0		2.8	0.9	

[a] nd = not detected
[b] Figures for urinary organic acids at time of admission are means and ranges in eight samples over 3 days

carnitines extracted from urine gave a spectrum (Fig. 3) in which the major ion not associated with the glycerol matrix used had a mass (m/z) of 246. High resolution mass measurements (Fig. 4) showed the identification of this ion to be consistent with isovalerylcarnitine, and this was confirmed by comparison with a synthesised standard. The changes in acylcarnitines observed during these studies thus can be ascribed to changes in isovalerylcarnitine concentration.

In the 24 h following the carnitine load there was no significant alteration in the urinary excretion of isovalerylglycine or

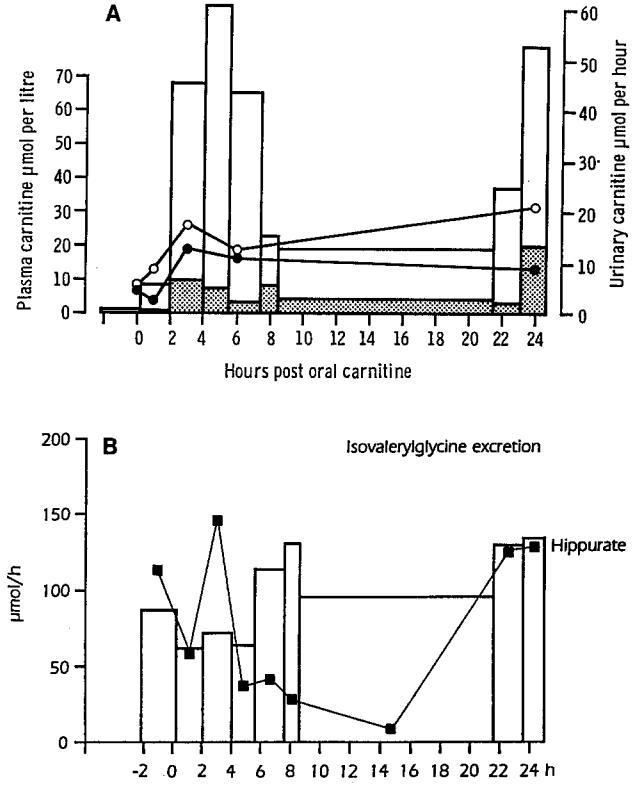

Fig. 2A, B. Plasma and urinary carnitines. (**A**) [● = free carnitine; ○ = acylcarnitines in plasma], and urinary isovalerylglycine and hippurate (**B**) following 200 mg/kg oral L-carnitine. Plasma values are concentrations (μmol/l). Urinary values are an excretion rate (μmol/h)

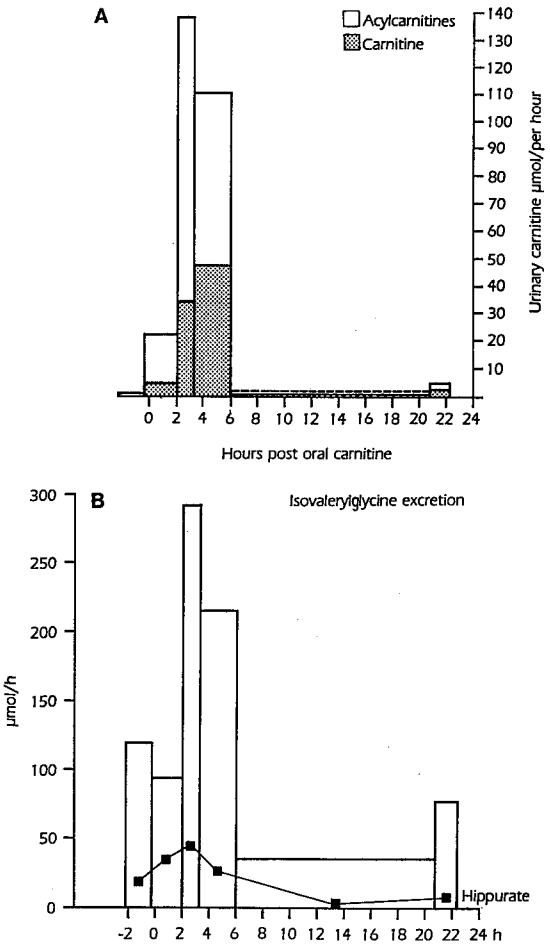

Fig. 3A, B. Urinary carnitines (**A**), and urinary isovalerylglycine and hippurate (**B**) following 200 mg/kg oral L-carnitine whilst receiving supplemental glycine

of any other abnormal metabolites. Excretion of hippurate and 4-hydroxy-hippurate did however change markedly (Fig. 2B).

Response to glycine

Regular administration of oral glycine 300 mg/kg per day was commenced in four divided doses. Plasma glycine levels rose to a maximum value of 1680 μmol/l. Isovalerylglycine in plasma rose to 14 μmol/l. Isovalerylglycine excretion showed a small but not statistically significant increase ($P = 0.17$) over a 4 day period [mean excretion ($n = 8$) before commencing treatment was 1980 and at the end ($n = 8$) 2441 mmol/mol creatinine]. However, the patient became increasingly lethargic and ataxic during this time and for this reason supplementary glycine was withdrawn after 5 days.

Response to carnitine during glycine therapy

A further 200 mg/kg L-carnitine was administered orally as a single dose whilst the patient was on regular glycine therapy. Once again there was a rise in urinary total carnitine excretion most marked in the excretion of acylcarnitines (Fig. 3A). On this occasion isovalerylglycine excretion rose to a peak of 5316 mmol/mol creatinine, a figure twice as large as was seen during the previous 2 days of glycine therapy (mean 2441, range 1400–3701 mmol/mol creatinine in eight samples) (Fig. 3B). There was no change in the excretion of the other abnormal metabolites, but there was an increase in the excretion of 4-hydroxyhippurate.

The response to carnitine and dietary therapy

The patient was commenced on a diet with a protein intake restricted to 2 g/kg per day corresponding to a leucine intake of approximately 185 mg/kg per day. She was also given orally regular L-carnitine 40 mg/kg per day in three divided doses. Urinary excretion of organic acids and carnitine were monitored over a 4 month period (Table 2). Urinary isovalerylglycine excretion was generally lower towards the end of this period. Throughout this time she excreted larger than normal amounts of carnitine, and acylcarnitine excretion was increased in particular. Analysis of plasma carnitines at the end of this 4 month period showed total carnitine to be normal (32.2 μmol/l), although free carnitine was low (14.9 μmol/l) and acylcarnitines were raised (17.3 μmol/l) [normal values for 2–5 years olds ± 1 S.D. are respectively 34.2 (± 3.8), 29.5 (± 4.3) and 4.6 (± 3.4) μmol/l, ($n = 15$)].

The patient has remained well on this combination of a moderate dietary restriction and L-carnitine therapy. She has continued to grow normally and her appetite remains good. She still has a slight general developmental delay and a Ruth Griffiths development assessment at 3 years 2 months gave a GQ of 81. She had another episode of intercurrent illness, not associated on this occasion with ketoacidosis, but during which her acylcarnitine:free carnitine ratio rose to 20.8 (Table 2).

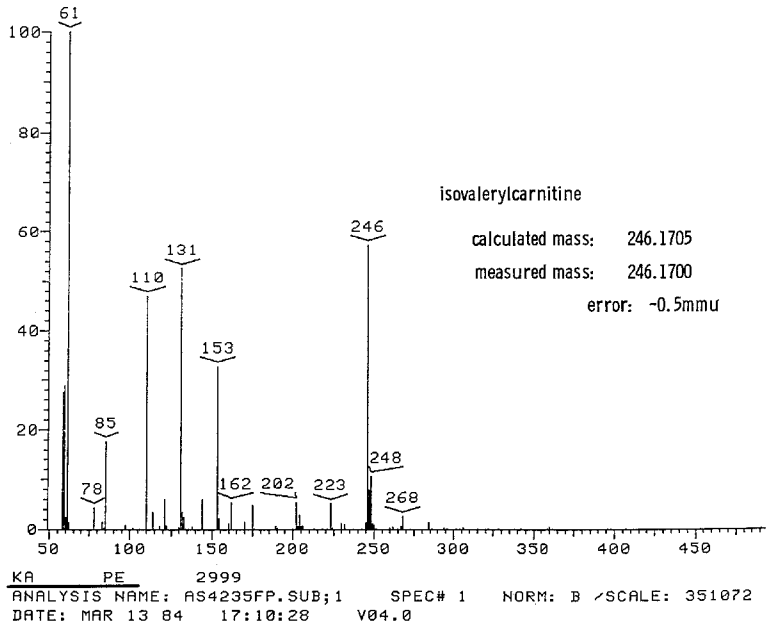

Fig. 4. Mass spectrum obtained by fast atom bombardment of a urine specimen obtained following an oral L-carnitine load. The major acylcarnitine was identified as isovalerylcarnitine

Table 2. Urinary carnitine and isovalerylglycine excretion during combined carnitine and dietary therapy

	Duration of therapy in days										Normal[c] (mean ± SD)
	0	36	43	50	57	67 (Admission to hospital with acidosis)	78	85	92	109	
Free carnitine (mmol/mol creatinine)	6.3[a] (1.7–14.8)	42.0	47.8	70.7	50.6	8.6	108.7	40.6	26.6	55.4	12.2 (± 7.6)
Acyl carnitines (mmol/mol creatinine)	14.6[a] (9.3–39.4)	321.9	229.1	392.2	293.3	178.3	112.9	250.2	331.2	325.0	15.1 (± 3.2)
Acyl/free ratio	3.6[a] (2.7–4.9)	7.7	4.8	5.5	5.8	20.8	1.0	6.2	12.9	5.9	
Isovalerylglycine (mmol/mol creatinine)	1980[b] (1510–2646)	2388	2086	1378	1962	1723	788	1132	1343	1904	

[a] Mean of five samples + range
[b] Mean of eight samples + range
[c] Normal subjects not receiving carnitine supplementation

Discussion

The patient described here has the clinical features of the intermittent, chronic form of isovaleric acidaemia. Her illness during the second week of life was not severe or life-threatening, although in retrospect it may have been the first manifestation of her disorder. During her first 2 years she contracted both chickenpox and measles and yet did not develop a severe illnes or coma on either occasion. However, analysis of her urine during an acute episode identified several of the metabolites previously described as being typical of the "neontal form" of isovaleric acidaemia. Several facts call into question this distinction between two forms of the disorder. Many patients who have only been diagnosised in late infancy may already have had repeated and unexplained bouts of illness, some of them with proven ketoacidosis [4, 9, 12, 18]. Some patients have had a moderately severe presentation in the newborn period [10] and others survive the fulminant neonatal illness and go on to have an intermittent chronic form of the disorder [11]. Therefore it is inappropriate to talk of an early and a late onset, neither can two distinct groups of patients be identified by the age at clinical *presentation*. It is much more likely that there is a spectrum of disease with the timing and severity of the presenting episode determined by environmental factors, by the amount of residual enzyme activity and by the modifying effects of the different enzymatic phenotypes in different individuals. Similarly these factors will determine which metabolites are excreted at different times in the same individual. This may help to explain the observation that certain metabolites are not found in large amounts in the earlier part of a ketoacidotic episode and that their maximum excretion may lag behind the peak plasma isovaleric acid level [15].

Plasma carnitine deficiency and the excretion of large quantities of acylcarnitines in the urine have been described in patients with a number of disorders of organic acid metabolism [6, 7]. It is suggested that supplementation with L-carnitine may be of benefit, especially in disorders of branched-chain amino acid metabolism. Our patient clearly had low plasma levels of carnitine with high plasma acylcarnitines and

a high urinary excretion of acylcarnitines. Following an oral load of carnitine she excreted large amounts of isovalerylcarnitine and her total plasma carnitine was restored to a normal level. There was no immediate effect on the urinary excretion of isovalerylglycine or of any other abnormal metabolites except for a rise in the excretion of hippurate and 4-hydroxyhippurate.

Carnitine may exert an effect in more than one way. By forming isovalerylcarnitine which is then excreted in the urine, it may detoxify the mitochondrion of accumulating isovaleryl CoA. The amount of isovalerylcarnitine excreted in the urine following an L-carnitine load (of 200 mg/kg) was 481 μmol/24 h, rather less than the 1972 μmol/24 h of isovalerylglycine excreted following the commencement of oral glycine (300 mg/kg per day). Supplemental L-carnitine did however cause an increase in the excretion of isovalerylcarnitine as evidenced by a more than ten-fold rise in urinary acylcarnitine concentration, whereas supplemental glycine alone did not increase significantly the excretion of isovalerate groups as isovalerylglycine. Another way in which supplemental oral carnitine might exert an effect is by altering the intramitochondrial acyl CoA:free CoA ratio in favour of CoA thereby stimulating the activity of key mitochondrial processes (such as tricarboxylic acid cycle activity) [6, 14].

The observations that glycine N-acylase has a high affinity for isovaleryl CoA [2] and that isovalerylglycine is a major metabolite in isovaleric acidaemia [1] had led to the use of glycine therapy. Krieger and Tanaka [12] found glycine administration to be of help in managing an acute ketoacidotic episode in isovaleric acidaemia although long-term administration failed to prevent ketoacidotic episodes which were induced by infections. Others [8, 15, 20] have also found glycine to be of benefit to their patients. Duran et al. [9] however rejected the use of glycine in two patients with a particularly mild form of this disorder because of the high glycine N-acylating capacity of their patients and the difficulties in administering glycine during acute ketoacidotic episodes. The clinical response of our patient to glycine suggests a further reason to be hesitant about the use of glycine. After 5 days of therapy at a dose similar to that used in previously reported cases she began to show encephalopathic features. These symptoms resolved shortly after stopping supplementary glycine and were almost certainly due to hyperglycinaemia. Despite a large increase in plasma glycine the response in terms of isovalerylglycine excretion was disappointing with no significant increase above pre-treatment levels. When additional L-carnitine was administered, however, isovalerylglycine excretion rose more than two-fold. This suggests that, as long as plasma glycine is maintained at an adequate level, without necessarily giving pharmacological supplements, the concomitant administration of L-carnitine is a most effective method of potentiating the excretion of isovalerylglycine. These observations have led to the use of mild dietary restriction and supplemental L-carnitine for our patient. We suggest that this is an effective method of treating patients with isovaleric acidaemia.

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