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ORIGINAL ARTICLE

Treatment of acute decompensation of maple syrup urine disease in adult patients with a new parenteral amino-acid mixture

A. Servais · J. B. Arnoux · C. Lamy · A. Hummel · N. Vittoz · I. Katerinis · V. Bazzaoui · S. Dubois · C. Broissand · M. C. Husson · M. P. Berleur · D. Rabier · C. Ottolenghi · V. Valayannopoulos · P. de Lonlay

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Abstract
Background Acute decompensation of maple syrup urine disease (MSUD) is usually treated by enteral feeding with an amino-acid mixture without leucine (Leu), valine or isoleucine. However, its administration is ineffective in cases of gastric intolerance and some adult patients refuse enteral feeding via a nasogastric tube. We developed a new parenteral amino-acid mixture for patients with MSUD.
Methods Seventeen decompensation episodes in four adult patients with MSUD treated with a parenteral amino-acid mixture (group P) were compared to 18 previous episodes in the same patients treated by enteral feeding (group E).
Results The mean Leu concentration at presentation was similar in the groups P and E (1196.9 μmol/L and 1212.2 μmol/L, respectively). The mean decrease in the Leu concentration during the first 3 days of hospitalisation was significantly higher in group P than group E (p=0.0026); there were no side effects. The mean duration of hospitalisation was similar (4 vs. 4.5 days, p=NS). No patient in group P deteriorated whereas one patient in group E required dialysis.
Conclusion This new parenteral amino-acid mixture is safe and allows efficient Leu concentration decrease during acute MSUD decompensation episodes in adults. Its use avoids the need for nasogastric tube insertion.

Introduction

Classic maple syrup urine disease (MSUD) is caused by a deficiency of branched-chain keto-acid dehydrogenase. The enzyme defect results in marked increase of the branched-chain amino-acids (BCAA) leucine (Leu), valine, and isoleucine, and also 2-keto acids, in plasma, urine and cerebrospinal fluid. MSUD can be diagnosed by amino-acid

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A. Servais · A. Hummel · N. Vittoz · I. Katerinis
Department of Nephrology, Hôpital Necker-Enfants Malades AP-HP, Paris, France

A. Servais · J. B. Arnoux · A. Hummel · N. Vittoz · I. Katerinis · V. Valayannopoulos · P. de Lonlay
Université Paris Descartes, Paris, France

A. Servais · J. B. Arnoux · A. Hummel · N. Vittoz · I. Katerinis · V. Bazzaoui · S. Dubois · V. Valayannopoulos · P. de Lonlay
Reference Center for Inherited Metabolic Disorders, Hôpital Necker-Enfants Malades, AP-HP, Paris, France

C. Lamy · C. Broissand
Department of Pharmacy, Hôpital Necker-Enfants Malades, AP-HP, Paris, France

V. Bazzaoui · S. Dubois
Department of Dietetic, Hôpital Necker-Enfants Malades, AP-HP, Paris, France

M. C. Husson · M. P. Berleur
AGEPS, AP-HP, Paris, France

D. Rabier · C. Ottolenghi
Department of Biochemistry, Hôpital Necker-Enfants Malades, AP-HP, Paris, France

A. Servais (✉)
Service de Néphrologie adultes, Hôpital Necker,
149 rue de Sèvres,
75015 Paris, France
e-mail: aude.servais@nck.aphp.fr

chromatography. The long-term treatment of patients with MSUD involves restriction of dietary BCAA to the amount that can be directly incorporated into body protein. This severely restricted diet includes adequate amounts of energy and other nutrients and normal to high amounts of non-branched-chain amino-acids, provided by synthetic BCAA-free amino-acid mixtures, allowing protein synthesis. Acute intercurrent episodes of decompensation are prevented by early recognition and treatment of situations that may lead to protein catabolism. During acute metabolic decompensations, cerebral oedema and brain-stem compression may cause unexpected death, whereas prolonged imbalances of circulating amino acids may have more subtle, and lasting, effects on brain structure and function (Ogier de Baulny H et al 2012). Thus, acute episodes of metabolic decompensation in patients with MSUD are medical emergencies. They may result from dietary deviation, insufficient intake of calories or amino acids (anorexia, fasting), injury or infection (Strauss et al 2010). The nutritional principles for treatment of acute episodes, even in severe cases, are similar to those applied in maintenance therapy: immediately exclude Leu from the diet and promote protein synthesis to reduce Leu concentrations in blood rapidly. BCAA-free amino-acid mixtures are essential to facilitate the incorporation of excess of Leu into new proteins, thereby reducing its circulation concentration and avoiding its toxic effects. BCAA-free amino-acid mixtures are administered with carbohydrate polymers and lipids, usually by nasogastric tube feeding.

In patients who present with gastric intolerance, the absorption of the BCAA-free amino-acid mixture is problematic, and possible only with a slow continuous nasogastric drip. The supply of isoleucine and valine has to be adjusted to their plasma concentrations.

However, during episodes of gastro-enteritis, this approach to treatment usually fails such that therapeutic management is difficult. Dialysis has been used to eliminate Leu and toxic metabolites efficiently. However, extracorporeal dialysis techniques are associated with complications and risks, including infection. They also require expertise and are not always available in all centres. During catabolic episodes complicated by high plasma leucine concentrations, the dilemma is whether to start dialysis or opt for medical management. The choice is difficult because it is not possible to identify patients in whom life-threatening central nervous system complications will develop if dialysis is delayed. To circumvent these problems and avoid dialysis, we developed and evaluated a new parenteral amino-acid mixture devoid of BCAA. Here, we present a comparison of the efficacy and tolerance of this new treatment with those of standard enteral feeding via nasogastric tube in MSUD patients suffering from metabolic decompensation. In particular, we followed the plasma Leu concentration decrease during the first 3 days of the acute episode, considered to be the period of highest risk of central nervous system complications.

Methods

Patients

Adult patients with "classic" MSUD with neonatal onset were included. In our institution, patients undergo regular monitoring of plasma Leu levels using blood spots on filter paper. In cases of catabolic disease, peripheral venous blood is assayed for Leu and the patient immediately starts an emergency diet containing no natural protein. In cases of clinical deterioration with anorexia and/or gastric intolerance, diarrhoea, infection, or if Leu concentration levels are above 763 μmol/L (10 mg/dL), the patient is hospitalised. Appropriate clinical and laboratory assessments are performed to detect dehydration, infection, metabolic acidosis, and ketosis and a new blood sample is taken and assayed for Leu. Patients with a plasma Leu concentration of more than 1525 μmol/L (20 mg/dL) and/or with neurological symptoms are immediately treated with dialysis. Patients without neurological symptoms and plasma Leu concentrations below 1525 μmol/L are treated medically with a diet. The goal of the treatment is to reduce the plasma Leu concentration to below 381 μmol/L (5 mg/dL) and the patients are usually discharged when this is attained.

The parenteral BCAA-free amino-acid mixture became available in our institution in 2010. Since then, adult patients admitted for a decompensation were prospectively treated with this new parenteral treatment (group P). We compared decompensations treated with this new parenteral treatment to previous decompensations treated with the enteral treatment in the same patients (group E). Decompensation episodes with incomplete data (e.g. plasma Leu concentrations not available) were excluded from the analysis. Plasma amino acids were assayed daily and the intake of the BCAA-free amino-acid mixture, valine and isoleucine was adapted accordingly. Valine and isoleucine were given enterally.

This study was approved by the institutional ethical committee.

Treatment

The parenteral BCAA-free amino acid mixture (*Acides aminés pour leucinose décompensée AP-HP*) is produced by the *Agence Générale des Equipements et Produits de Santé* (AGEPS), public pharmaceutical establishment of AP-HP (Paris hospitals) in France. It is packed in 500 ml bags, and contains 200 kcal per litre and 52 g of amino acids per litre (Table 1). It may be stored at ambient temperature, under 25 °C. It may be infused through a peripheral intravenous line. The recommended dose is 1 to 2 g per kilogram of body weight per

Table 1 Comparative nutritional information of parenteral and one enteral branched-chain amino-acids-free amino-acid mixtures

BCAA-free amino-acid mixture AP-HP			MSUD 2 secunda® (Milupa)[a]		
Ingredients		Average content per 1000 mL	Ingredients		Average content per 100 g
Energy	kcal	200	Energy	kcal	290 kcal
Amino acids	g	52	Amino acids	g	84
Alanine	g	6.3	Alanine	g	4.0
Arginine	g	4.1	Arginine	g	3.5
Aspartic acid	g	4.1	Aspartic acid	g	9.8
Cysteine	g	1.0	Cystine	g	2.3
Glutamic acid	g	7.1	Glutamic acid	g	20.6
Glycine	g	2.1	Glycine	g	2.3
Histidine	g	2.1	Histidine	g	2.3
Lysine	g	5.6	Lysine	g	6.9
Methionine	g	1.3	Methionine	g	2.3
Phenylalanine	g	2.7	Phenylalanine	g	4.1
Proline		5.6	Proline	g	9.2
Serine	g	3.8	Serine	g	5.2
Taurine	g	0.3	Taurine	—	
Threonine	g	3.6	Threonine	g	4.6
Tryptophan	g	1.4	Tryptophan	g	1.8
Tyrosine	g	0.5	Tyrosine	g	5.0
			Carnitine	mg	150
Daily price for an adult 70 kg (dose 1.5 g per kg per day)		191 euros	Daily price for an adult 70 kg (dose 1.5 g per kg per day)		271 euros

[a]MSUD 2 secunda also contains mineral and trace elements, maltodextrin, vitamin mixture and vanillin. BCAA, branched-chain amino-acids

day (a volume of 1000 to 1500 ml per day in most cases). The collection of data on adverse effects was performed using standard forms which were completed by clinicians and examined by the AGEPS, and its drug monitoring unit. The only contra-indications are those usually applied for any parenteral solution. Enteral feeding through a nasogastric tube involved 1 to 2 g per kilogram of body weight of one of the following BCAA-free amino-acid mixtures: MSUD 2 secunda® (Milupa) or Maxamum MSUD® (SHS-Nutricia). Comparative nutritional information of the parenteral and one enteral BCAA-free amino-acid mixture is presented in Table 1.

All patients received oral valine and isoleucine supplementation, adjusted to plasma concentrations determined daily. Additional enteral and/or intravenous energy was provided by glucose (10 % glucose polymers or IV solutions) and lipid solutions (20 % of olive oil or IV Intralipid® or Kabiven®), the choice of enteral and/or parenteral route depending on gastric tolerance and hunger.

Biochemistry

Leucine, valine and isoleucine levels were measured daily at 8 o'clock in the morning on blood samples taken on the arm opposite to the infusion. They were immediately brought to the laboratory. The parenteral solution was administered continuously and not switched off.

Plasma amino acids were analysed by exchange chromatography with a JEOL Aminotac Analyser.

Statistical analysis

Continuous data are reported as means ± SD. Dichotomous data are presented as percentages. The chi-square test and the Fisher's exact test were applied for dichotomous and categorical data, respectively, and the unpaired *t* test was used to compare continuous variables. Repeated measures two-way ANOVA was used to compare the curves of mean leucine concentration decrease in the two groups. Two-tailed p values <0.05 were regarded as statistically significant. Statistical analyses were performed using InStat 3 ® and Prism 4® software.

Results

Clinical presentation

Clinical data are presented in Table 2.

Four adult patients (three men and one woman), between 21, and 31 years of age, were included in the group of

patients treated with the parenteral mixture (group P). They presented a total of 17 decompensation episodes in 2010. These 17 episodes were compared to 18 decompensation episodes treated by enteral feeding in the same four patients between 2005 and 2010 (group E). Four other episodes during the same period were excluded from analysis because of missing data. The higher frequency of decompensations in 2010 than previously was due to psychiatric problems in two patients.

In group E, ten decompensation episodes were due to diet deviation, three to infection, two to anorexia, and two to other causes. In group P, six decompensation episodes were due to diet deviation, three to infection, five to anorexia, and four to other causes.

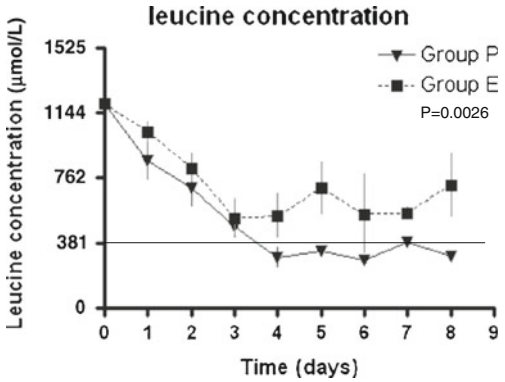

Fig. 1 Comparison between the decrease in mean leucine concentration in the enteral (E) and in the parenteral (P) groups (p=0.026 by two way ANOVA). Mean ± SEM

Leucine concentration outcomes

On admission, the plasma Leu concentration ranged from 670.9 to 1608.6 µmol/L (8.8 mg/dL to 21.1 mg/dL) in group E and from 792.9 to 1684.8 µmol/L (10.4 mg/dL to 22.1 mg/dL) in group P: the mean Leu concentration was similar (1196.9±312.6 µmol/L in group E versus 1196.9± 289.7 µmol/L in group P, p=NS) (Table 2).

The mean plasma Leu concentration in group E decreased during the first 3 days but did not normalise before hospital discharge due to poor dietary compliance (Fig. 1). Indeed, in seven cases the patients were discharged from hospital against medical advice before Leu concentrations had normalised (< 381 µmol/L).

The amount of supplemental isoleucine or valine administered was based on the plasma levels and ranged from 600 to 900 mg of isoleucine per day and 400 to 600 mg of valine per day. Thus, mean isoleucine and valine concentrations were maintained within the normal range (191 to 381 µmol/L and 213 to 427 µmol/L, respectively).

In group P, mean plasma Leu concentrations decreased and in most cases normalised (<381 µmol/L) within 3.5 days (Fig. 1). However, in four cases they did not normalise because the patient was discharged before normalisation, against medical advice. The decrease in the plasma Leu concentration was significantly greater in group P than group E (Fig. 1, p=0.0026, by two-way ANOVA).

The mean duration of hospitalisation was similar for groups E and P (3.7±0.9 days vs. 4.1±1.9 days), partly because some patients were discharged before normalisation of the Leu concentration. Mean Leu concentration at discharge was 343.1±236.3 µmol/L (range 53.4–907.2) in group E and 320.2 ±129.6 µmol/L (range 76.2–602.3) in group P.

Table 2 Clinical and biological presentation and evolution

	Group E	Group P
Age (years)	25.2±5.1 (21–31)	
Body mass index (kg/m^4)	22.9±5.8 (16.3–28.1)	
Episodes of decompensation (N)	18	17
Leucine concentration on day 0 (µmol/L)	1196.9±312.6 (670.9–1608.6)	1196.9±289.7 (792.9–1684.8)
Time to normalisation of Leu concentration, if normalisation (days)	3.4±1.0 (2–6)	3.8±1.8 (1–8)
Duration of hospitalisation (days)	3.7±0.9 (3–6)	4.1±1.9 (1–8)
Discharge from hospital before normalisation (N)	7	4
Leucine concentration at discharge (µmol/L)	343.1±236.3 (53.4–907.2)	320.2±129,6 (76.2–602.3)
Enteral feeding refusal (N)	4	—
Dialysis (N)	1	0
Calories (kcal/day)	4812±994	4687±364
Amino acids (g/day)	78.3±26.4 (56–118)	73.4±10.2 (52–78)

N, number; mean ± SD (range). Group E, episodes treated by enteral feeding; group P, episodes treated by parenteral administration of the new amino-acid mixture devoid of leucine, valine, and isoleucine

Clinical complications

In group E, patients refused enteral feeding by nasogastric tube in four episodes. In these cases, the patients received their usual amino-acid mixture orally and additional calories as oral and/or intravenous carbohydrates and lipids. In one of these cases, the patient had to be dialysed due to the emergence of neurological signs.

Energy and amino acid intakes

The mean calorie intake was similar in the two groups: 4812 ±994 kcal/day (group E) and 4687±364 kcal/day (group P); p=NS. Patients received 78.3±26.4 g/day of amino acids in group E and 73.4±10.2 g/day in group P.

Tolerance

No side effects were observed in group P. Percutaneous intravenous peripheral catheters were used in all but one patient in whom an intravenous central catheter had to be used because of poor venous access.

Discussion

Acute decompensations of MSUD are life-threatening and require rapidly efficient treatment. We developed a new parenteral BCAA-free amino-acid mixture for the treatment of such acute episodes, and present here safety and efficacy data in comparison with those of "classic" treatment by enteral feeding in an adult MSUD patient population.

The decrease in the mean plasma Leu concentration during the first 3 days of hospitalisation was significantly greater following parenteral treatment with the new BCAA-free amino-acid mixture (group P) than following standard enteral treatment (group E). Furthermore, no patient in group P required dialysis whereas one patient in group E underwent dialysis for increasing Leu concentrations and the occurrence of neurological signs.

Enteral feeding is currently the cornerstone of medical treatment of acute decompensation in MSUD patients (Ogier de Baulny H et al 2012). However such treatment is impossible in cases of gastric intolerance. This situation is particularly frequent in paediatric patients. Furthermore, many of the adult patients we manage refuse enteral feeding by nasogastric tube. In such cases, including one episode described in this study, dialysis is required. Parenteral administration of a BCAA-free amino-acid solution is a potentially useful alternative to enteral emergency diet and dialysis. It may avoid both the need for special procedures other than a peripheral intravenous line and the potential complications of dialysis. Furthermore, due to the logarithmic model of clearance during dialysis, it has been shown in the paediatric population that once leucine levels are around 1000 μmol/L the rate of clearance slows down significantly and addition of amino acids becomes essential to enhance clearance (Jouvet et al 2005). This further supports use of the BCAA-free amino-acid solution even in patients on dialysis or heamofiltration.

In our study, the use of the BCAA-free amino-acid mixture effectively reduced plasma Leu levels in acutely ill patients with MSUD and was associated in all cases with clinical improvement and resolution of the acute episode.

Some authors have described locally developed intravenous solutions containing mixtures of essential and non-essential amino acids but devoid of Leu, valine, and isoleucine (Townsend and Kerr 1982; Berry et al 1991; Nyhan et al 1998). Townsend et al were the first to use total parenteral nutrition successfully as an alternative therapy for an acutely ill newborn with MSUD who was unable to feed and in whom peritoneal dialysis failed (Townsend and Kerr 1982). Berry et al treated nine episodes of acute illness in five children (including one newborn) intravenously with a BCAA-free amino-acid solution (Berry et al 1991): this parenteral nutrition successfully reduced plasma Leu levels in all cases.

In both our series and all reported cases of use of parenteral nutrition with amino-acid mixtures without Leu, valine and isoleucine, there was a substantial fall in plasma Leu concentrations and concomitant clinical improvement. Although it is possible that the observed decline in plasma BCAA levels under the parenteral nutrition is the consequence of a shift of branched-chain amino acids from the extracellular to the intracellular compartment, there is evidence that the decline is due to increased protein synthesis. Indeed, the rate of nitrogen retention in the neonate treated with parenteral nutrition by Townsend et al matched published rates of protein accretion in infants of the same age; and the administration of more calories alone was not sufficient to decrease Leu levels in the absence of amino acid administration in one of the patients described by Berry et al (Townsend and Kerr 1982; Berry et al 1991).

We compared parenteral treatment using an intravenous BCAA-free amino-acid solution with previous enteral treatment with BCAA-free amino-acid solution for decompensations episodes in the same patients. The decrease of mean Leu concentrations was higher during the 3 first days of parenteral treatment than that of enteral treatment. Furthermore, the treatment was better tolerated and accepted than nasogastric tube insertion by the patients.

We were unable to compare the time required to normalise Leu levels or the duration of hospitalisation between the two groups because some patients with psychiatric problems presenting with repeated decompensation episodes discharged themselves from hospital and follow-up, against medical advice, before normalisation of Leu levels.

A high calorie intake must be provided as a complement to the amino-acid mixture (Strauss et al 2010). Indeed, patients in both treatment groups were given more than 4500 kcal per day. The guidelines that we followed for the emergency treatment also include supplementation with valine and isoleucine to prevent deficiency. Indeed, plasma levels of isoleucine and valine must be maintained above the physiological range at the outset of acute therapy to compete effectively with the high levels of Leu transport into cells (Smith et al 1987). Failure to provide sufficient isoleucine, valine, and other essential amino acids for protein synthesis slows the rate of Leu depletion.

Our study evidences the simplicity, safety and efficacy of parenteral nutrition with a new solution during metabolic decompensation episodes and demonstrates the potential benefit for adult, and probably child, MSUD patients. Infusion bags (500 ml) are readily available from AGEPS for 94.5 euros and may be exported with authorisations of health agencies. Compared to other therapies the cost is unlikely to be a limiting factor. Given the spectre of central nervous system complications (i.e. cerebral oedema and death) this therapy should be considered for all acutely ill patients with elevated plasma Leu concentrations, especially in the case of gastric intolerance or refusal to be treated through a nasogastric tube. The widespread use of this new parenteral BCAA-free amino-acid mixture would facilitate the care of, and reduce the risk of complications in, MSUD patients presenting with acute metabolic decompensation.

Conflict of interest None.

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