Treatment of the Acute Crisis in Maple Syrup Urine Disease

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**Background:** The acute crisis of metabolic decompensation in maple syrup urine disease is a potentially lethal medical emergency that requires reduction in concentrations of leucine and other branched-chain amino acids in plasma. Experience with intravenous mixtures of amino acids indicates that this can be accomplished by the synthetic forces of protein synthesis. However, these intravenous mixtures are not generally available.

**Objective:** To develop enteral mixtures suitable for administration by nasogastric drip in minimal volume.

**Design:** Mixtures of amino acids were designed containing no leucine, isoleucine, or valine for administration by nasogastric drip. Needs for water and calories were to be met intravenously. They were designed to be used in the management of the acute crisis.

**Setting:** Inpatient pediatric service.

**Patients:** Two patients with maple syrup urine disease. Data were collected during the management of 3 episodes of metabolic imbalance.

**Intervention:** Studies were carried out for 4 to 11 days, during which there was no intake of leucine. Four different mixtures were used and a fifth was designed on the basis of this experience.

**Main Outcome Measures:** Effects on the concentrations of leucine and the other branched-chain amino acids. Clinical status closely mirrored the concentration of leucine.

**Results:** In each instance, a progressive fall in leucine concentration was obtained. Rates of fall were comparable to those obtained with intravenous therapy. Concentrations of isoleucine fell to levels that made this amino acid limiting for protein synthesis and hence therapeutic effect. This led to greater and earlier supplementation with isoleucine. Valine supplementation was also useful.

**Conclusions:** The acute crisis of metabolic imbalance in maple syrup urine disease may be effectively treated by the continuous intragastric drip of solutions of amino acids devoid of leucine along with provision of water and calories intravenously.

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**Editor’s Note:** We will, on occasion, publish a well-designed and well-implemented study involving a relatively rare disease to assist those who provide general pediatric care to children with these disorders.

_Catherine D. DeAngelis, MD_
PATIENTS, MATERIALS, AND METHODS

PATIENTS

Two boys had presented in the neonatal period with the classic picture of MSUD. Their routine maintenance regimens contained 0.25 to 0.5 mg/kg of whole protein, calculated to contain 24 to 48 mg/kg of leucine. At the time of study patient 1 was a 9-year-old Filipino American boy who had had exemplary compliance with the dietary regimen since the initial neonatal episode, displayed normal steady-state concentrations of branched-chain amino acids, and had not required admission to the hospital for almost a year. His weight was 45 kg. Patient 2 was an Hispanic American boy admitted to the hospital at ages 2 and 3 years; his compliance left much to be desired. He seldom had a plasma concentration of leucine less than 400 μmol/L and had had many admissions to the hospital. His weight was 18.5 kg in the first episode and 21 kg in the second. The initiation of each of the episodes studied seemed to be caused by acute viral illness, which was self-limited.

PREPARATIONS AND PROTOCOL

Each enteral preparation was prepared from free amino acids (Spectrum Chemical, Gardena, Calif). Alanyl-glutamine was obtained from Ajinomoto USA, Teaneck, NJ. Each preparation (preparations 1-5, Table) was prescribed in a dose of 2 g/kg of total amino acids per day. The data for 4 commercial preparations (Ketonex-1 and Ketonex-2, Ross Laboratories, Columbus, Ohio, and MSUD-1 and MSUD-2, Mead Johnson) are listed in the Table for comparison. Amino acid solutions were prepared daily by adding 32 to 90 g of mixture to 300 to 720 mL of sterile water (0.1-0.125 g/mL of amino acids) to which was added half a teaspoon (0.01-0.004 g/mL) of salt. Solutions were fed via nasogastric tube at the rate of 12 to 30 mL/h depending on the size of the child and tolerance. Feedings were continuous and deliberately low in volume to minimize the possibility of emesis. Initial feeds were given at half the prescribed rate and advanced after 2 to 3 hours of demonstrated tolerance to full volume. If emesis occurred, feedings were discontinued for one half to 1 hour, restarted at the previously tolerated rate, and advanced appropriately. Caloric support was given as 10% dextrose intravenously. Additional calories were supplied as polyose or Mead Johnson 80056 by nasogastric tube after the patient's intestinal tolerance had been demonstrated and additional volume could be tolerated. Caloric feedings were adjusted independently from the continuous drip of amino acids.

Plasma concentrations of amino acids were determined with a Beckman automatic amino acid analyzer at baseline and at intervals following the initiation of treatment.

A reasonable alternative approach is to harness the forces of anabolism and protein synthesis by providing energy and a mixture of amino acids lacking leucine, isoleucine, and valine, such that these accumulated amino acids are laid down into protein, reducing levels in extracellular fluid and reversing toxic effects. Saudubray et al have calculated that the anabolic effect of a gain in body weight of as little as 50 g would lead to an incorporation of sufficient leucine (1000 mg) into protein to decrease the plasma concentration by 3000 µmol/L (40 mg/dL). Accordingly, we and others have developed intravenous solutions containing mixtures of essential and nonessential amino acids devoid of leucine, isoleucine, and valine for this purpose. The response has been rewarding. In each instance there has been a dramatic linear fall in concentrations of leucine and the other branched-chain amino acids and concomitant improvement in clinical condition. The use of these solutions is ideal, especially in a patient with vomiting, but they are expensive and seldom promptly available.

For these reasons there has been interest in the use of enteral solutions for this purpose. Parini and colleagues reported the successful management of 8 episodes in 5 patients with nasogastric drip feeding of a formula free of branched-chain amino acids; we have had the same experience. In each case, standard MSUD formula was used without added protein. Even in a patient who is vomiting usual feedings, it is sometimes possible to achieve tolerance with a slow continuous nasogastric drip. However, experiences with this approach convinced us that this method was less than optimal. In the best example, the patient was admitted to the hospital because of intractable vomiting associated with intercurrent infection. The projected time delay made intravenous therapy unrealistic for prompt reversal of his metabolic imbalance. It was elected to hydrate him intravenously and to provide amino acids, minus the branched-chain amino acids, as standard MSUD (Mead Johnson, Evansville, Ind) formula in the usual dose of 2 g/kg of amino acids. To achieve minimal volume for a vomiting patient and still avoid hyperosmolarity, a concentration of 1 calorie per milliliter was used. This required a volume of 100 mL/h, which is far from optimal even by slow drip in a patient who is vomiting. Recovery was slow, and there was some continued vomiting. Commercial formulas are designed for oral nutrition in a patient in a steady state and contain large amounts of sugar, fat, and electrolytes, along with the amino acids. It seemed pertinent to design mixtures for enteral use in which amino acids only could be administered slowly in minimal volume by nasogastric tube, providing water, electrolytes, and calories intravenously. This approach has now been used successfully in the management of several episodes of acute metabolic imbalance in 2 patients with MSUD.

The composition of the various preparations is given in the Table. The initial amino acid composition was taken from that of the intravenous solution that had been developed for the acute management of MSUD and modified.

- tabolism, which is counterproductive. They also require expertise, particularly in their application to very young infants, that may not always be available.
fied on the basis of monitoring concentrations of amino acids in blood and urine. This amino acid profile had proven effective not only in reducing plasma concentrations of branched-chain amino acids, but also in assuring normal concentrations of the other amino acids during the course of treatment, suggesting that the proportions were optimal. The exclusion of alanylglutamine in preparation 3 was because of a temporary lack of availability.

The progressive changes from preparations 1 to 5 were made on the basis of results of amino acid analyses. The changes from 1 to 2 were an increase in aspartic acid after finding low plasma levels and reduction of threonine because of high concentrations in blood and loss in urine. Preparations 3 and 4 differed only in the availability of alanylglutamine. Salt was added to solutions 3 and 4 only in an attempt to promote better absorption; however, theoretically it should be advantageous to provide additional sodium. Preparation 5 has not yet been used, but it has been decided to add isoleucine from the beginning of treatment; regular experience with these preparations and the intravenous solution has shown that the rapid fall in concentrations of isoleucine to very low levels leads to a situation limiting protein synthesis. Isoleucine supplementation is regularly required well before leucine levels become normal. The amino acid in greatest concentration in these mixtures is alanine, and the amounts of alanine were adjusted depending on the other amino acids. A goal was to provide approximately one fourth to one third of total nitrogen from alanine. This has also been true of our intravenous solutions.11 The rationale was the excellent tolerance for this amino acid and, in contrast to some other amino acids, its unlikelihood to be toxic, as well as the demonstration17,18 of the unique anabolic properties of alanine.

In these studies, tolerance to nasogastric feeding was excellent. Emesis was minimal. There was no diarrhea. Neither of the patients required peritoneal dialysis or hemodialysis. The course of patient 1 is shown in Figure 1. Concentrations of leucine prior to therapy approximated 1000 µmol/L. Within 48 hours the concentration was 306 µmol/L, and the next day it was 227 µmol/L. This rate of fall of 773 µmol/L in 48 hours is consistent with reported results12 obtained with intravenous therapy. At 48 hours the concentration of isoleucine was 12 µmol/L, despite the fact that supplementation with 2 mg/kg of isoleucine and 2 mg/kg of valine had been initiated 14 hours earlier. The concentration of isoleucine was 60 µmol/L on the following day. The concentration of alanine prior to therapy was close to 100 µmol/L; it rose with therapy to 600 to 800 µmol/L.

Two episodes of patient 2 are shown in Figure 2. In the first (Figure 2, left), the concentration of leucine prior to treatment rose to 1332 µmol/L. Concentrations of isoleucine and valine approximated 200 and 400 µmol/L, respectively, and that of alanine was as low as 78 µmol/L. He was treated with preparation 1 for the first day and preparation 2 thereafter. The concentration of isoleucine was 12 µmol/L, despite the fact that supplementation with 2 mg/kg of isoleucine and 2 mg/kg of valine had been initiated 14 hours earlier. The concentration of isoleucine was 60 µmol/L on the following day. The concentration of alanine prior to therapy was close to 100 µmol/L; it rose with therapy to 600 to 800 µmol/L.

<table>
<thead>
<tr>
<th>Amino Acids, mg</th>
<th>Preparation Used in This Study</th>
<th>Preparations Commercially Available in the United States*</th>
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<tr>
<td>Alanine</td>
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<td>155</td>
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<tr>
<td>Arginine</td>
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<td>Aspartic acid</td>
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<td>Carnitine</td>
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<td>Cystine</td>
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<td>Glutamine†</td>
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</tr>
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<td>Glutamic acid</td>
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<td>152</td>
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<tr>
<td>Glycine</td>
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<td>Leucine</td>
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<td>Tryptophan</td>
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<tr>
<td>Valine</td>
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<tr>
<td>Total Amino Acids</td>
<td>1040</td>
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</table>

* Ketonex-1 and Ketonex-2, Ross Laboratories, Columbus, Ohio; MSUD-1 and MSUD-2, Mead Johnson, Evansville, Ind. NA indicates not available.
† Glutamine was provided as alanylglutamine.
Men promote protein synthesis and net removal of leucine from the plasma.

We believe that this approach along with intravenous therapy should supplant dialysis in the management of most of these patients. Peritoneal dialysis has been shown to be inconsistent, as measured by leucine content of the dialysate. In at least 2 reported instances, no leucine was found in the dialysate. Furthermore, in those patients for whom peritoneal dialysis is successful in removing branched-chain amino acids, there is a tendency to reach a plateau level of 1000 to 1500 µmol/L after 24 hours, and it has been suggested that it is not useful to prolong dialysis beyond this time.8 Hemodialysis is clearly more effective. In an experience with a single patient,7 7 hours of intravenous glucose failed to improve the concentration of leucine appreciably, while 3 hours of hemodialysis led to a fall from 2630 to 1418 µmol/L. Of course, this level too is representative of marked metabolic imbalance, and repeated hemodialysis was required at 16 hours. Clearances by hemodialysis were approximately 10 times those reported for peritoneal dialysis.7 It is unlikely that hemodialysis would become routine for every instance of metabolic imbalance in a patient with MSUD. It could be reserved for patients with life-threatening cerebral edema, cardiovascular abnormalities, or renal imbalance. The approach we have reported is consistent with the development of relatively normal levels of leucine within 24 to 48 hours of initiation of therapy.

The regimens explored have considerable advantages over currently available commercial preparations. The main issue is that commercially available formulas, designed for steady-state feeding in which they are mixed with whole protein, contain only 11% to 13% of calories from amino acids. During acute episodes in MSUD in which vomiting is the rule rather than the exception, the amounts of amino acids that can be supplied to promote anabolism are severely limited. Caloric concentration and osmotic load are such that to provide sufficient quantities of amino acids to have a positive effect, the volume that must be supplied becomes limiting. This is particularly difficult as the child gets older. The high osmolality of the formulas is partly due to the electrolyte, vitamin, and mineral composition, but the caloric content of fat and carbohydrate is also substantial. In the acute situation the requirements for energy, electrolytes, and water can be met intravenously, reserving the nasogastric feeding for an optimal mixture of amino acids.

The commercial preparations do not seem to have optimal amino acid profiles for the promotion of anabolism. Again, they are designed to be used with whole proteins. Our mixtures have been designed to be complete amino acid mixtures except for leucine, isoleucine, and valine. They contain large amounts of gluconogenic amino acids, essentially alanine, in an attempt to suppress protein catabolism (which would further increase plasma concentrations of branched-chain amino acids) and promote anabolism. Alanine has been shown9 to have a unique role as an inhibitory coregulator of intracellular degradation of proteins. Glutamine

This experience adds further weight to the argument14 that anabolism is sufficient to reverse the metabolic imbalance that occurs acutely in MSUD. These patients were treated early when levels of leucine had risen to 1000 to 1300 µmol/L, but it is clear from the observations of Paresi et al14 and our own15 that even levels higher than 3000 µmol/L are successfully treated in this way. Thompson and colleagues19 have demonstrated that this type of regimen promotes protein synthesis and net removal of leucine from the plasma.

Figure 1. Amino acid management of acute maple syrup urine disease in patient 1. Preparations 1 and 2 were used (see Table for composition of preparations).

[Table and graph showing amino acid management, with peaks and troughs for leucine, isoleucine, and valine concentrations over time.

8.7 mg/kg. With this regimen the concentration of threonine was as high as 603 µmol/L; the amount of threonine in the preparation was reduced, and the concentration fell to 178 µmol/L. Concentrations of glutamine ranged from 400 to 507 µmol/L during the study. It was concluded that the rate of fall in leucine in this episode was slower because the supply of extra isoleucine in adequate amounts was delayed.

In the second episode (Figure 2, right) the pretreatment concentration of leucine was 1165 µmol/L. By 24 hours the level was 720 µmol/L but that of isoleucine was 28 µmol/L and the next day a value of 0 µmol/L was recorded. The rate of fall of leucine levels had slowed to 626 µmol/L. Vigorous supplementation of 15 mg/kg of isoleucine and 10 mg/kg of valine restored levels of each and leucine levels fell to 100 µmol/L, again demonstrating the importance of providing sufficient quantities of isoleucine.

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is an important energy source for the intestinal mucosa and other rapidly dividing cells. Glutamine uptake by intestine is increased in response to stress.21 Pools of free glutamine are decreased following injury or infection.22 Glutamine is not present in commercial sources of free amino acids for enteral or parenteral alimentation. Thus, there may be a deficiency of glutamine under conditions of critical illness. The absence of glutamine in available solutions is a consequence of its instability; it is rapidly converted nonenzymatically to pyroglutamic acid (oxoproline) at room temperature and neutral pH. In contrast, dipeptides of glutamine are quite stable, even under conditions of heat sterilization; we and others9-11,23 have shown that their incorporation into parenteral alimentation solutions leads to a positive nitrogen balance and support of free concentrations of glutamine in plasma. Among the peptides studied, alanylglutamine was superior.24 In designing these solutions we endeavored to supply a complete mixture for the management of acute metabolic imbalance. At the same time, we recognize that the acute management of this imbalance is short-term therapy and it is unlikely that a source of glutamine is necessary for this use.

Our experience with these enteral mixtures and intravenous solutions has indicated that the provision of large amounts of calories may not be necessary to promote the anabolic response. Berry et al12 used large amounts of glucose, which necessitated placement of central lines and the administration of insulin. Wendel and colleagues25 have used the anabolic effects of glucose and insulin as sole therapy for acute metabolic imbalance in this disease. In our patients, caloric intake ranged from 65 to 100 kcal/kg. The objective was to provide 200 mL/kg of 10% glucose and 2 g/kg of amino acids, which would have provided 88 cal/kg. This should be an adequate amount for a patient immobile in bed. In fact, basal metabolic expenditure in patients weighing 45 and 18.5 kg would be 30 to 45 cal/kg. It is also possible that large amounts of alanine served to spare some energy requirements by turning off the alanine-glucose cycle and limiting breakdown of muscle protein.

The need for a full complement of amino acids to have successful anabolism is highlighted by the development of low concentrations of isoleucine and valine. This may slow or stop the fall in leucine concentration, as observed in this study and that of Parini et al,14 or even lead to a rise in the concentration of leucine. Supplementation with isoleucine and valine is virtually always required prior to achieving normal levels of leucine. We attribute the difference between results in patient 1 and patient 2 to the availability of isoleucine and valine, as indicated by plasma levels. These observations point out how essential it is in the acute management of MSUD to monitor the concentrations of amino acids in plasma, especially isoleucine and valine. Parini and colleagues14 have recommended maintaining concentrations of isoleucine and valine higher than 100 µmol/L, but we have never seen problems as long as levels are higher than 50 µmol/L. The amounts of

![Figure 2. Amino acid management of acute maple syrup urine disease in patient 2. Left, Episode 1. Right, Episode 2. Preparations 3 and 4 were used in episodes 1 and 2, respectively (see Table for composition of preparations).](https://jamanetwork.com/)
supplemental isoleucine and valine used in this study ranged from 2 to 15 mg/kg. The former figure is a low representation of our initial experience; it was chosen because patient 1 was a somewhat obese 45-kg child. Recently we have begun with 10 mg/kg. The ultimate amounts should be determined by the concentrations of these amino acids observed. In the presence of very low levels, it is preferable to use larger doses that can be reduced after demonstrated success than to impede overall therapy with too little.

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