The nutritional management of urea cycle disorders

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Diet is one of the mainstays of the treatment of patients with urea cycle disorders. The protein intake should be adjusted to take account of the inborn error and its severity and the patient's age, growth rate, and individual preferences. Currently, the widely used standards for protein intake are probably more generous than necessary, particularly for those with the more severe variants. Most patients, except those with arginase deficiency, will need supplements of arginine, but the value of other supplements including citrate and carnitine is unclear. Any patient on a low-protein diet should be monitored clinically and with appropriate laboratory tests. All should have an emergency (crisis) regimen to prevent decompensation during periods of metabolic stress. (J Pediatr 2001;138:S40-S45)

In a normal Western diet, more protein is eaten than is necessary for growth and development. The waste nitrogen can only be stored temporarily and therefore has to be excreted. Although many different nitrogenous compounds are present in the urine, the major vehicle for nitrogen excretion is urea. With increasing protein intake there is a linear increase in urea production.[1] Control of urea synthesis is complex, involving induction of the enzymes of the urea cycle and other factors.[2] The maximum flux through this pathway is reduced in patients with inborn errors of the urea cycle[3,4] so the pathway cannot meet all the demands placed on it. The result is accumulation of compounds that buffer and transport surplus nitrogen, notably glutamine and alanine. Consequently, one of the mainstays of treatment of patients with urea cycle disorders is the reduction of the nitrogen intake. Ideally, the aim would be to give just that which is needed for growth and maintenance without any excess. However, that proves not to be possible.

Tissue protein is constantly being synthesized and broken down. During growth there is net protein synthesis, but during fasting and illness degradation will exceed synthesis with negative nitrogen balance and increased flux through the urea cycle. When protein intake is reduced, protein synthesis falls, and while protein degradation and amino acid oxidation also decrease, the decline is less. Thus at a critical protein intake, degradation exceeds synthesis. The clinical consequence is that even on the minimum protein intake that will support normal growth, there is always some flux through the urea cycle.

Protein Requirements

The normal protein requirements vary with age. In very early infancy the requirements exceed 2 g/kg/d, but they fall rapidly in the first year. The standard recommendations that are widely used are those of the Food and Agriculture Organization/World Health Organization/United Nations University (1985).[5] These are presented as the average ("total") nitrogen requirement and the mean +2 SD (Table I). This represents the "safe" intake for most individuals, because it will meet the requirements for >97% of the population. However, for most infants, including those with urea cycle disorders, it will provide more protein than is absolutely necessary. These standards have been revised downward in recent years (Table I).[6] Because urea production and excretion are linearly related to protein intake,[1] the load on the urea cycle will also be reduced by reducing the protein intake. A decrease in the protein intake of 0.1 g/kg/d will reduce waste nitrogen by 16 mg N/kg/d.

The protein intake of each patient must be adjusted to the individual needs and should take account of several factors. These include the patient's age and growth rate and that of the inborn error and its severity. For those with severe variants, some of the nat-

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0022-3476/2001/$35.00 + 0 **9/0/111835**
doi:10.1067/mpd.2001.111835

Table I. Protein requirements by age expressed as grams per kilogram per day

Age	FAO/WHO/UNU 1985* Mean (total)	FAO/WHO/UNU 1985* Safe (mean + 2SD)	Revised (Dewey et al 1996)† Mean (total)	Revised safe values (Dewey et al 1996) †Safe (mean + 2SD)
Months				
0-1	-	-	1.99	2.69
1-2	2.25	-	1.54	2.04
2-3	1.82	-	1.19	1.53
3-4	1.47	1.86	1.06	1.37
4-5	1.34	1.86	0.98	1.25
5-6	1.3	1.86	0.92	1.19
6-9	1.25	1.65	0.85	1.09
9-12	1.15	1.48	0.78	1.02
Years				
1-1.5	1.0	1.26	0.79	1.0
1.5-2	0.94	1.17	0.76	0.94
2-3	0.91	1.13	0.74	0.92
3-4	0.88	1.09	0.73	0.9
4-5	0.86	1.06	0.71	0.88
5-6	0.83	1.02	0.69	0.86
6-7	0.82	1.01	0.69	0.86
7-8	0.81	1.01	0.69	0.86
8-9	0.81	1.01	0.69	0.86
9-10	0.8	0.99	0.69	0.86
Girls				
10-11	0.81	1.0	0.71	0.87
11-12	0.79	0.98	0.69	0.86
12-13	0.77	0.96	0.69	0.85
13-14	0.75	0.94	0.68	0.84
14-15	0.72	0.9	0.66	0.81
15-16	0.7	0.87	0.66	0.81
16-17	0.66	0.83	0.63	0.78
17-18	0.64	0.8	0.63	0.77
Boys				
10-11	0.79	0.99	0.69	0.86
11-12	0.79	0.98	0.69	0.86
12-13	0.81	1.0	0.71	0.88
13-14	0.78	0.97	0.69	0.86
14-15	0.77	0.96	0.69	0.86
15-16	0.74	0.92	0.68	0.84
16-17	0.72	0.9	0.67	0.83
17-18	0.69	0.86	0.66	0.81

FAO/WHO/UNU, 1985.
Dewey et al, 1996.
FAO, Food and Agriculture Organization; *WHO,* World Health Organization; *UNU,* United Nations University.

ural protein (a mixture of essential and nonessential amino acids) may be replaced with an essential amino acid mixture (Table II). When one of these is given, surplus nitrogen is used to synthesize nonessential amino acids, thereby reducing the load on the urea cycle. The composition of the amino acid mixtures varies, and their use should form part of the overall nutritional strategy. Unfortunately, no controlled trials to determine the value of different doses and composition have been done.

Arginine

In normal children and adults, arginine is not an essential amino acid be-

Table II. Composition of essential amino acid supplements

Constituents/100 g	Dialamine	UCD 1	UCD 2	Cyclinex-1	Cyclinex-2
Protein equivalent (g)	25	56	67	7.5	15.0
Energy (kcal)	360	250	290	515	480
Carbohydrate (g)	65	5.8	4.4	52	40
Fat (g)	0	0	0	27	20.7
Amino acids (g)					
Cystine	1.2 (0.23)	3.1 (0.24)	Trace (<0.1)	0.3 (0.14)	0.6 (0.14)
Histidine	1.2 (0.23)	3.1 (0.24)	3.6 (0.24)	0.36 (0.17)	0.72 (0.17)
Isoleucine	3.3 (0.64)	7.6 (0.59)	8.9 (0.59)	1.28 (0.59)	2.56 (0.59)
Leucine	5.13 (1.00)	12.8 (1.00)	15.0 (1.00)	2.17 (1.00)	4.34 (1.00)
Lysine	4.2 (0.82)	9.0 (0.70)	10.7 (0.71)	1.11 (0.51)	2.22 (0.51)
Methionine	1.2 (0.23)	3.1 (0.24)	7.1 (0.47)	0.34 (0.16)	0.68 (0.16)
Phenylalanine	1.8 (0.35)	5.3 (0.41)	14.1 (0.94)	0.75 (0.35)	1.5 (0.35)
Threonine	3.6 (0.70)	6.0 (0.47)	7.1 (0.47)	0.75 (0.35)	1.5 (0.35)
Tryptophan	0.75 (0.15)	2.2 (0.17)	2.8 (0.19)	0.28 (0.13)	0.56 (0.13)
Tyrosine	3 (0.58)	6.5 (0.51)	Trace (<0.1)	0.88 (0.40)	1.76 (0.40)
Valine	4.62 (0.90)	9.0 (0.70)	10.7 (0.71)	1.43 (0.66)	2.86 (0.66)
Other constituents: all products have added vitamins and minerals				Carnitine Taurine	Carnitine Taurine

Ratio to leucine shown in parentheses.

cause it is synthesized by the urea cycle. However, in those with inborn errors of the urea cycle (except arginase deficiency), this amino acid becomes indispensable or at least semiessential, because the rate of synthesis may not meet requirements.[7] In carbamyl phosphate synthetase deficiency and ornithine transcarbamylase deficiency, the requirements are usually considered as 100 to 170 mg/kg/d.[7] In severe variants of these disorders, arginine may be replaced by citrulline because it has the added advantage that an additional atom of nitrogen is used in the synthesis of arginine. The conversion of 175 mg (1 mmol) of citrulline uses 14 mg (1 mmol) of waste nitrogen.

Within the urea cycle, ornithine is reformed with each turn of the cycle. In citrullinemia (argininosuccinic acid synthetase) deficiency and argininosuccinic aciduria (argininosuccinic acid lyase) deficiency, ornithine is not reformed because of the metabolic block. To maintain the integrity of the cycle, the ornithine must be replaced. In one study the dose necessary to replenish the ornithine was 2.2 mmol/kg/d (380 mg/kg/d).[8] Larger arginine doses of up to 4 mmol/kg/d (700 mg/kg/d) may be given to neonates,[9] but it is not clear whether such large doses are necessary in older patients. This therapy will increase not only the concentrations of ornithine but also those of citrulline and argininosuccinate in argininosuccinic acid lyase, respectively. There appears to be no evidence of major complications as a result of the high concentrations of these compounds.[10,11] However, subtle cognitive deficits cannot be excluded. The widely accepted view is that hyperammonemia is likely to be more detrimental than are increased concentrations of citrulline or argininosuccinate.

Because argininosuccinate contains 2 "waste" nitrogen atoms and a renal clearance equal to the glomerular filtration rate,[12] the losses of this compound create an alternative pathway of nitrogen excretion. In patients with argininosuccinic aciduria, approximately 40% of urinary nitrogen is in the form of argininosuccinate and related compounds.[13]

Other Supplements

Early studies of citrate showed that it reduced postprandial elevation of ammonia, and it has been suggested that it may replenish aspartate in argininosuccinic aciduria with improved short-term metabolic control.[14,15] However, the long-term value is unclear.

In hyperammonemic rats L-carnitine increases brain and hepatic adenosine triphosphate, acetyl, and free CoA concentrations.[16] In some studies neurologic symptoms and toxicity have been reduced,[17-19] but not in others.[20] Reduced plasma carnitine concentrations in rats and infants with urea cycle disorders have been described.[21,22] However, although the use of carnitine is advocated by some, there are no systematic studies in humans, and its therapeutic value in these disorders is uncertain.

MONITORING TREATMENT

As with any low-protein diet, care must be taken to ensure that the diet is nutritionally complete. For practical purposes a low-protein diet means low-quality protein, and care must be taken to ensure that the amino acid intake is balanced and that the intake of all the essential amino acids is adequate. Although there is a risk of essential amino acid deficiency, there is probably a greater risk of micronutrient deficiency, particularly iron and zinc. Complete vitamin and mineral supplements will correct the low intake provided the patients take them, but they are widely disliked.

It is important to ensure that energy intake is adequate. Many patients are anorexic and may not only have a low protein intake but an energy deficit as well. However, giving more energy than is necessary will not reduce protein catabolism further and will merely lead to obesity.

The diet should be monitored clinically and with laboratory investigations. The former should include general health and well-being, growth, and liver size. Of the laboratory investigations, plasma ammonia and quantitative analysis of amino acids are useful. Urine orotate may also be helpful in ornithine transcarbamylase deficiency. None of these tests is perfect. Plasma ammonia is subject to numerous factors or artefacts that affect the recorded levels. These include physiological variables such as protein intake, timing of last meal, and poor or difficult sample collection. This does not make it a good index of long-term control. Plasma glutamine is generally regarded as a better guide. In some patients there is a clear correlation between the plasma ammonia and glutamine concentrations,[23,24] but this is not always the case (J.V. Leonard, unpublished observations). Decompensation may be associated with a rise in plasma glutamine.[23,25] However, high glutamine concentrations do not invariably indicate incipient encephalopathy (J.V. Leonard, unpublished observations). Nevertheless, it seems prudent to aim to keep the plasma glutamine concentration to <1000 μmol/L. Other nutritional and hematologic markers may be indicated, particularly if the metabolic control is poor, or the patient is not thriving or is not taking his or her vitamin and mineral supplement. These would include serum (or plasma) prealbumin, transferrin, ferritin, vitamin B_{12} (or urine methylmalonate), zinc, and copper. Other tests may also be necessary, depending on the individual problem.

The plasma arginine concentration should be between 50 and 200 μmol/L, and the concentrations of essential amino acids should be monitored as a guide that protein intake is adequate. Although there are dangers of undertreating patients, overtreating patients, particularly those with mild disease, should also be recognized.

EMERGENCY MANAGEMENT

Although good metabolic control can be achieved for most patients, apart from some of those with the most severe variants, all are at risk of decompensation with metabolic stress. This includes fasting, intercurrent illness, particularly gastroenteritis, anesthesia, and protein load such as gastrointestinal hemorrhage. Plasma ammonia concentrations may rise rapidly, and it is essential that all patients should have an emergency (or crisis) regimen.[26] Whenever patients are at risk, they should have high-energy low-protein intakes. This intake should be given orally but, if not tolerated, then it should be given intravenously at an early stage. Medicines should continue to be given orally or intravenously and increased, if necessary. The family must recognize when the child is at risk[27] and have clear instructions about the nutritional management required during these periods.

CONCLUDING REMARKS

Diet is one of the mainstays of the treatment of patients with urea cycle disorders. It must be adjusted to meet the child's requirements as closely as possible. Some patients with these disorders have an aversion to protein, whereas others do not. Those on the stricter diet may need less medication than those on a more liberal diet. This concept of a balance is important. All diets must be monitored carefully, and a clear plan for the nutritional treatment of the patient during metabolic stress is essential.

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NUTRITIONAL MANAGEMENT DISCUSSION

Protein Requirements

For many years the Food and Agriculture Organization/World Health Organization/United Nations University guidelines[1] have been used as the standard for calculating daily protein requirements. For patients with urea cycle disorders, these guidelines will generally provide more protein than is really necessary or tolerated, and therefore the use of revised, lowered estimates of protein requirement[2] was discussed and generally agreed by the conference participants. Lower dietary protein intake will reduce the amount of waste nitrogen that must be excreted.

After birth, the aim is to stabilize the child on a protein intake of 1.5 g/kg/d by the time of discharge, but this often means starting off at a lower level (0.5 to 0.7 g/kg/d) and gradually increasing the protein intake to avoid recurrent hyperammonemia. Protein requirements of a newborn baby change markedly in the early months, with a "honeymoon" period, during which a high-protein intake is well tolerated. At approximately 6 months the requirements, when expressed in terms of body weight, decrease. However, when lower amounts of protein are prescribed, there are challenges knowing how much should be given, particularly in the recovery phase after a hyperammonemic episode.

Various parameters are monitored to confirm that the protein intake is adequate. These include clinical features such as the growth of the patient, the appearance of the hair, skin, and nails, and biochemical tests including the plasma concentration of ammonia, essential amino acids, and glutamine, hemoglobin, hematocrit, albumin, prealbumin, transferrin, and total protein.

Monitoring, clinically, biochemically, and nutritionally, should be continuous. The lower the protein intake is, the more meticulous the monitoring must be. Any changes to a diet are made in an incremental manner (by no more than 10% at any one time). Plasma amino acids may take between 2 to 5 days to re-equilibrate, so monitoring changes in the diet at 1- to 2-week intervals is appropriate. When patients, even those with severe defects, are clinically stable, there is some flexibility in giving additional protein without causing an increase in their blood ammonia or glutamine. However, for patients who are doing poorly, there is no flexibility, because their metabolic status may deteriorate rapidly.

Patients with mild ("leaky") defects who have some residual enzyme activity may show marked improvement in their protein tolerance in the early

months because of an upregulation in the enzymes and an increase in the numbers of cells expressing the enzyme.

In patients with no residual liver enzyme activity, management requires administration of essential amino acids, but there are currently no good guidelines on how much should be given. The current practice is to monitor the parameters discussed earlier and intervene, if necessary, based on the results of the patient's growth and biochemical investigations. Twenty-five to 50% of total protein intake may be given as essential amino acids.

If a patient is not on an adequate diet, and the plasma ammonia concentration is satisfactory, the dietary protein may be increased. However, if the ammonia and glutamine levels are high, possibly caused by insufficient protein or calories, the nutritionist should be able to analyze the diet and determine the likely cause.

Guidance to Parents

Detailed guidance about the patient's needs in terms of the calories, protein, and fluid intake is essential for parents. The pharmacologic treatment of patients with urea cycle disorders entails the use of drugs which, in their oral formulations, are not palatable. To minimize problems with feeding and medication, it is considered important that families of children with urea cycle disorders should be trained in the use and placement of nasogastric feeding tubes. These can be used to ensure that the child receives appropriate nutritional intake and medication. In one center the number of hospital admissions has been reduced by 70% since this training has been given.

Dietary Supplements

The discussion on dietary supplements highlighted the lack of good information in this area. Children on modular feeds will not need supplementation with vitamins or minerals, but it was generally recognized and agreed that micronutrient status should be studied when the clinical picture suggested this was necessary. Requirements for many trace elements and vitamins in children with urea cycle disorders have not been established.

Several of the supplements appear to be very low in vitamin B_{12}, and even if the babies are taking their feeds, there may not be enough vitamin B_{12} in the their diet. Some centers measure urinary methylmalonic acid to monitor the adequacy of this supplement.

Decompensation

It is now recognized that boys with mild disease may decompensate during puberty and at this stage have a particularly high morbidity. Once through this period, they often have few problems.

Glutamine Levels

It is not clear why such disparate outcomes are seen in individuals with similar glutamine levels. There may be a genetic component to this.

There are 2 ways of addressing raised glutamine concentrations. One is to reduce the protein intake, and the other is to give more medication. Relying purely on glutamine levels as the basis for treatment may lead to excessive reduction in protein intake, thus inhibiting normal growth, or to giving too much medication.

Furthermore steady-state levels of glutamine do not differ between patients who are or are not taking Ucephan, but there is a higher nitrogen flux in those who do. Each patient may have an optimal glutamine level, and it may not be justified to use a concentration of 1000 μmol/L as the upper limit over which therapy should be adjusted in all individuals. However, there are no data on which to base any firm recommendations.

Arginine and Carnitine Supplementation

Arginine supplements are given routinely to patients with urea cycle disorders. Arginine supplementation was an early method of treating hyperammonemic coma, and the use of intravenous arginine is covered in the article by Batshaw, MacArthur, and Tuchman elsewhere in this supplement. Recommended doses of arginine (3 to 4 mmol/kg/d) have not been associated with serious adverse events, but there is concern that arginine supplementation may not be as harmless as previously thought, and that increases in arginine blood levels may contribute to toxicity.

Fewer than half of the participants at the conference prescribe carnitine supplements to their patients. The protective effect of carnitine supplementation is based on work in hyperammonemic mice, but the evidence that it is of therapeutic benefit in humans has not been demonstrated.

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