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Presentation and Management of Urea Cycle Disorders Outside the Newborn Period

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Proceedings of a symposium conducted in Toronto, October 25 and 26, 2004. Supported by an unrestricted educational grant from Ucyclyd Pharma, a division of Medicis Pharmaceutical Corporation, Scottsdale, Arizona.

October 2005 • Volume 21 • Number 4S

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CRITICAL CARE CLINICS
October 2005
Editor: Joe Rusko

Volume 21, Number 4S
ISSN 0749-0704

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Critical Care Clinics (ISSN 0749-0704) is published quarterly by W.B. Saunders Company. Corporate and editorial offices: Elsevier Inc., 1600 John F. Kennedy Blvd., Philadelphia, PA 19103-2899. Accounting and circulation offices: 6277 Sea Harbor Drive, Orlando, FL 32887-4800. Periodicals postage paid at Orlando, FL 32862, and additional mailing offices. Subscription prices are $170.00 per year for US individuals, $280.00 per year for US institution, $85.00 per year for US students and residents, $210.00 per year for Canadian individuals, $340.00 per year for Canadian institutions, $230.00 per year for international individuals, $340.00 per year for international institutions and $115.00 per year for Canadian and foreign students/residents. To receive student/resident rate, orders must be accompanied by name of affiliated institution, date of term, and the *signature* of program/residency coordinator on institution letterhead. Orders will be billed at individual rate until proof of status is received. Foreign air speed delivery is included in all *Clinics* subscription prices. All prices are subject to change without notice. POSTMASTER: Send address changes to *Critical Care Clinics*, W.B. Saunders Company, Periodicals Fulfillment, Orlando, FL 32887-4800. **Customer Service: 1-800-654-2452 (US). From outside of the US, call 1-407-345-1000. E-mail: hhspcs@harcourt.com**

Critical Care Clinics is also published in Spanish by Editorial Inter-Medica, Junin 917, 1er A, 1113, Buenos Aires, Argentina.

Critical Care Clinics is covered in *Index Medicus, EMBASE/Excerpta Medica, Current Concepts/Clinical Medicine, ISI/BIOMED,* and *Chemical Abstracts.*

Printed in the United States of America.

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Crit Care Clin 21 (2005) S27–S35

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Nutritional Management of Urea Cycle Disorders

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A cardinal principle of urea cycle disorder (UCD) management is the restriction of protein intake to minimize the flux of nitrogen through the urea cycle. However, the calculation of tolerated protein intake is neither simple nor static. Tissue protein is constantly being synthesized and catabolized, and ammonia detoxification needs vary according to enzyme deficiency, growth rate, activity level, and the patient's developmental and health status. During growth, increased protein intake is necessary to prevent catabolism. Careful protein management is also essential during hospital treatment when a patient may receive only parenteral nutrition and is subjected to long intervals of bed rest, which can contribute to breakdown of tissue protein. Administration of essential and other amino acids must also be considered in the nutritional equation, as should the appropriate titration of nitrogen-scavenging medications, energy intake, and vitamin and mineral supplements. In addition, the patient's own eating behaviors, lifestyle, and life events may often confound even the most carefully balanced prescription.

In both acute and long-term situations, close monitoring and calibration of the relevant factors are critical to preventing metabolic decompensation. This, in turn, is essential to maintaining existing neurologic status and providing the patient (and patient's family) with a reasonable quality of life. This paper presents two case histories and a series of recommendations outlining the nutrition management of urea cycle disorders. It also identifies difficulties that arise in the course of treatment, and suggests practical solutions for overcoming them.

Case 1

Inducing anabolism

Medical history

After an uneventful birth and successful breastfeeding for the first 2 days of life, a 3-day-old white girl exhibited lethargy and refusal to suck. Enzyme values reflecting liver function were mildly increased and her plasma ammonia concentration at 5 days of life was significantly elevated at > 500 μmol/L.

Further findings included abnormal urine lactic and pyruvic acids caused by shock and poor perfusion; elevated plasma amino acid concentrations, specifically citrulline (2694 μmol/L), glutamic acid, glutamine, alanine, methionine, lysine, and histidine; and excessive urine orotic acid. A diagnosis of citrullinemia (argininosuccinate synthetase [ASS] deficiency) was made.

Treatment

Treatment was started on day 5 at which time the patient's plasma ammonia concentration was 518μmol/L. To maximize caloric intake, the child received hyperalimentation via umbilical artery catheter. The regimen included dextrose 25% in water at 18 mL/hr, fat emulsion (Intralipid) 20% at 0.75 mL/hr (1 g/kg/d) as an energy source, and insulin 0.05 u/kg/d to promote nutrient use. In addition, she was given L-arginine HCL 10% 500 mg/kg/d, an amino acid

Dr. Summar acknowledges the support of NIH grants MOI-RR-0095 and U54-RR-019453.

Complete financial disclosure information for each author is provided in the frontmatter of this supplement on page iii.

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that becomes conditionally essential because of the decreased rate of synthesis by the urea cycle (in all urea cycle disorders except L-arginase deficiency). This prescription offered 112 kcals/kg/d and 0 g/kg/d of protein. Nitrogen scavenging was provided by sodium phenylacetate and sodium benzoate (Ammonul) 500 mg/kg/d. Within 24 hours, the plasma ammonia concentration had decreased to 80μmol/L.

On the ninth day of life (day 4 of treatment), the patient began transitioning to oral feeds and hyperalimentation fluids and intravenous medications were decreased. Starting with a hyperalimentation regimen of dextrose 25% in water 18 mL/hr, insulin 0.02 u/kg/d, essential and nonessential amino acid mixture (TrophAmine) 0.5 g/kg, fat emulsion (Intralipid) 20% 1g/kg/d, and L-arginine HCL 10% 500 mg/kg/d, she was gradually advanced to full oral feeds, including amino acid modified medical food with iron (Cyclinex-1) 25 g, protein-free diet powder with iron (ProPhree) 3 g, L-arginine base 27 mL (66.6 mg/mL) (after intravenous arginine was discontinued), and the oral nitrogen scavenger sodium phenylbutyrate (Buphenyl) 500 mg/kg/d.

Although her plasma citrulline concentration did not change significantly (Table 1), the patient showed general improvement in other important parameters. The plasma glutamine concentration decreased substantially and fell below the lower limit of the reference range. The other plasma essential amino acids, which include the branched chain amino acids, were in the reference ranges, although both leucine and isoleucine were near the lower end of the range. The patient was discharged when she was 12 days old.

Table 1
Plasma amino acid concentrations (μmol/L)

Amino acid	Patient at diagnosis	Patient after treatment	Patient at discharge	Reference range
Taurine	124	200	175	38–227
Aspartic acid	15	9	5	0–28
Threonine	83	75	299	50–248
Serine	127	53↓	95	90–209
Glutamic acid	209 ↑	67	52	10–189
Glutamine	2079 ↑	811	172↓	246–984
Proline	349	54↓	106	88–417
Glycine	253	16	265	125–497
Alanine	578 ↑	197	262	124–573
Citrulline	2694 ↑	1856 ↑	2260 ↑	6–52
Valine	195	97	153	67–299
Cystine	42	7	40	4–65
Methionine	160 ↑	26	49	17–49
Isoleucine	40	20	35	20–96
Leucine	108	47	63	29–151
Tyrosine	111	8↓	71	24–129
Phenylalanine	63	60	71	37–86
Ornithine	32	168	183 ↑	19–173
Lysine	464 ↑	77	224	43–243
Histidine	152 ↑	63	68	38–145
Arginine	26	258	16	20–149

Discharge regimen

It was imperative in the weeks and months following discharge that the infant ingest sufficient protein, energy, and other essential nutrients to ensure growth, but not so much protein that elevated ammonia levels or vomiting would result. With the advent of nitrogen scavenging medications, protein intake did not need to be as restricted as in the past. Care required a carefully calibrated diet, written instructions for ongoing management and dietary modifications during illness, and rigorous education of the parents regarding the necessity to adhere to the diet, the value of nasogastric feeds as needed, and the need for a rapid response to any signs of decompensation.

An age-appropriate diet was prescribed. The diet consisted of medical foods and infant formula which provided 1.9 g/kg/d of protein (54% protein from medical foods and 46% from Enfamil [Mead Johnson & Company, Evansville, Indiana]), 123 kcal/kg/d of energy, and 500 mg/kg/d of L-arginine base. This regimen supplied about 24 kcal/fluid ounce. Additional water (100 to 150 mL/d) was to be offered.

Parents were instructed how to insert a nasogastric tube in the event of a poor suck. In this case, formula was to be given every 3 hours, and sodium phenylbutyrate was to be administered every 6 hours. The parents were also provided with a letter at discharge that detailed the regimen to be used to prevent decompensation during periods of metabolic stress associated with infections and fevers. Symptoms they were instructed to look for included refusal to suck, labored breathing, lethargy, and excess sleepiness. Should the child appear ill, they were told to temporarily decrease or eliminate protein intake from food and substitute a special metabolic formula that would provide increased calories from non-protein sources, as well as necessary vitamins and minerals. They were also instructed to continue sodium phenylbutyrate, and to administer antiemetic medication and nasogastric feeding, if required. In the event that feeding was disrupted, the child was to be taken to the emergency room (ER) where the staff should be given a copy of the "emergency letter."

At age 2, a gastrostomy tube (g-tube) was placed to overcome the child's mild anorexia.

Outcome data

With sodium phenylbutyrate and diet management, plasma ammonia concentrations have been maintained in treatment range. As reflected in Table 2, the patient's protein and energy intake have been within the recommended guidelines throughout her life. Because a reduction in whole dietary protein alone does not usually offer adequate nutrients for growth, her diet has consistently provided about 50% of protein through supplementation with medical foods. This has not only provided higher concentrations of essential amino acids to take advantage of their lower nitrogen density, but also provided a source of vitamins and minerals, and additional calories from fats and carbohydrates. Such high essential amino acid protein sources

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Table 2
Recommended daily nutrient intake in urea cycle disorders

	Nutrient				
Age	Patient protein intake* (g/kg)	Protein (g/kg)	Patient energy intake* (kcal/kg)	Energy (kcal/kg)	Fluid (mL/kg)
Infants					
0 to <3 mo	2.1–1.4	2.20–1.25	150–101	150–125	160–130
3 to <6 mo	1.5–1.2	2.00–1.15	100–80	140–120	160–130
9 to <12 m	1.2–1.1	1.60–0.90	80–75	120–110	130–120
Girls and boys	(g/day)	(g/day)	(kcal/day)	(kcal/day)	(mL/day)
1 to <4 yr	18.6–12.5	8–12	800–1040	945–1890	945–1890
4 to <7 yr	21.0–19.0	12–15	1196–1435	1365–2415	1365–2445
7 to <11 yr	22.0–24.0	14–17	1199–1693	1730–3465	1730–3465
Women					
11 to <15 yr		20–23		1575–3150	1575–3150
15 to <19 yr		20–23		1260–3150	1260–3150
≥19 yr		22–25		1785–2625	1875–2625
Men					
11 to <15 yr		20–23		2100–3885	2100–3885
15 to <19 yr		21–24		2200–4095	2200–4095
≥19 yr		23–32		2625–3465	2625–3465

* Data are for Case 1 patient.
Modified from Acosta PB, Yannicelli S. Nutrition support protocols. Columbus, OH: Ross Products Division, Abbott Laboratories; 2001; with permission.

have helped meet all essential amino acid requirements. At 10 years of age, the child's growth continues to be satisfactory: height 25th percentile and weight 50th percentile.

Case 2

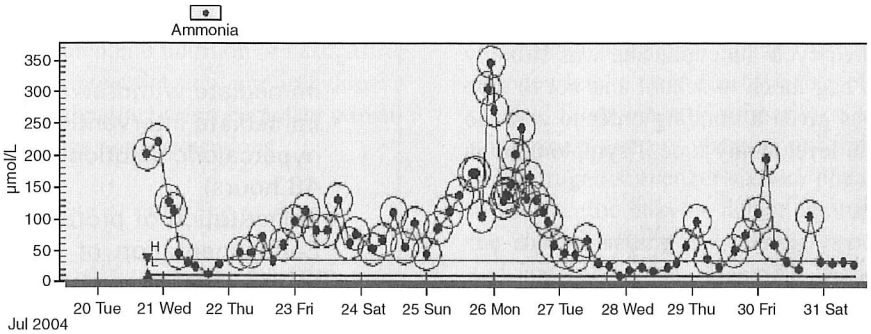
Onset of hyperammonemia

Medical history

A 10-year-old African-American female presented to a tertiary care ER with ataxia, disorientation, and mild hemiplegia. She had no known prior encephalopathic or other unusual episodes. She may have mildly self-restricted protein intake. She had reached menarche just 2 months before presentation. Her initial plasma ammonia concentration was 330μmol/L. A presumptive diagnosis of a urea cycle disorder was made and she was treated with intravenous sodium benzoate and sodium phenylacetate (Ammonul), L-arginine, and substantial IV and enteral carbohydrate intake. The plasma ammonia concentration dropped some 100 μmol/L in 2 hours, and soon returned to normal. However, it spiked twice over the next 5 days for no apparent reason, eventually tapering to normal. The girl suffered no intellectual deficit and was initially discharged on a regimen of protein restriction at 1.0 g/kg/d, sodium phenylbutyrate (Buphenyl) 308 mg/kg/d (20 g/d), and citrulline 108 mg/kg/d (7 g/d), the latter two dose levels represent the usual maximum adult dosage for her weight of 65 kg. She was later identified as a symptomatic carrier for ornithine transcarbamylase (OTC) deficiency; she had an affected male cousin in the maternal line.

Clinical course

Ten months later, the patient became progressively disoriented over 24 to 48 hours, shortly after her menses began. Upon admission, she exhibited a reduced level of consciousness. Her initial plasma ammonia concentration was between 200 and 225 μmol/L (Fig. 1). It was reduced to a normal concentration within 24 hours following administration of IV sodium benozoate and sodium phenylacetate (Ammonul) and L-arginine as before; the patient was then



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