

Protein Status of Infants with Phenylketonuria Undergoing Nutrition Management

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Objectives: The objectives of this study were to determine if Phenex-1, amino-acid modified medical food with iron maintained normal indices of protein status in infants with phenylketonuria (PKU) and to investigate factors that influence plasma amino acid concentrations.

Methods: A study was conducted for six months in 35 infants with classical PKU diagnosed in the neonatal period. Diet diaries and plasma amino acid concentrations were obtained monthly. Blood for analysis of plasma albumin, blood urea nitrogen (BUN), retinol binding protein (RBP) and transthyretin was obtained at one, three and six months of study.

Results: Mean (\pm SEM) total daily intake of medical food and nutrients was 79 ± 4 g; 17.3 ± 0.6 g protein, 660 ± 18 kcal, 255 ± 10 mg phenylalanine (Phe), and 1423 ± 56 mg tyrosine (Tyr). Mean concentrations of plasma amino acids, except cystine (during entire study), glycine (first month) and Phe were in the normal range. Mean concentrations of plasma Phe were in the treatment range (120 to 360 μ mol/L). Plasma concentrations of arginine, methionine, Phe, tryptophan, Tyr, and valine were positively correlated with intakes at various months of study. Concentrations of aspartic and glutamic acids, Phe, and Tyr were positively correlated and 17 amino acids were negatively correlated with the interval between feeding and blood draw. At six months of study, concentration of plasma albumin was 4.1 ± 0.1 g/dL, RBP was 3.74 ± 0.2 mg/dL, transthyretin was 17.9 ± 0.9 mg/dL, and urea nitrogen was 11.9 ± 0.5 mg/dL.

Conclusion: During study, all mean plasma indices of protein status were in normal reference ranges. Phenex-1 supports normal mean plasma amino acid, albumin, RBP, transthyretin, and BUN concentrations when fed in adequate amounts.

PKU is an inherited disorder of Phe metabolism characterized by an inability to normally metabolize Phe to Tyr. Without restriction of dietary Phe intake, Phe and its metabolites accumulate in blood and tissues and Tyr becomes deficient. These metabolic changes result in mental retardation, seizures and hyperactivity. Therapy consists of restricting dietary Phe to an

amount that results in near normal plasma Phe concentration. Tyr is supplemented in an effort to maintain normal plasma Tyr concentration. Nutrition management is accomplished through use of Phe-free elemental medical foods combined with intact protein to supply prescribed Phe.

Phe-free sources of protein are essential to the management

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of patients with PKU. However, L-amino acids, which are the source of approximately 75% of the dietary protein equivalent consumed by these patients [1], have not been adequately studied in infants to determine their efficacy in supporting protein status. Hanley et al. [2] reported hypoproteinemia in five of 32 infants treated with Lofenalac (Mead Johnson Nutritional, Evansville, Indiana), a casein hydrolysate. Many of the infants were not evaluated for protein status. Shenton et al. [3] reported that serum transthyretin (prealbumin) concentrations in 20 treated children with PKU, aged two to nine, were lower than in children from a normal group. Transthyretin concentrations have been reported in only a very small number of infants with PKU [4].

Plasma albumin concentrations fall only after significant protein depletion has occurred. RBP and transthyretin (half-lives of about twelve hours and two days, respectively) are sensitive indicators of visceral protein status and indicate possible problems in protein status long before plasma albumin concentration does [5]. The dearth of reported studies on the adequacy of L-amino acid mixtures to support indices of protein status in infants with PKU warranted evaluation of Phenex™-1, an amino acid modified medical food with iron (Ross Products Division, Columbus, Ohio).

Phenex-1 is formulated from synthetic L-amino acids, carbohydrate, fat, minerals and vitamins. The amino acid profile, except for deleted Phe and increased Tyr, is based on a composite of human milk and whole chicken egg. The purposes of this report are to describe protein status of infants with PKU-fed Phenex-1 and to describe some factors that influenced plasma amino acid concentrations.

MATERIALS AND METHODS

Ethical Considerations

The investigators obtained approval of the consent form and the study design from the institutional review boards at the participating medical school clinics and hospitals. Parents of all subjects signed informed consent forms.

Study Design and Subject Selection Criteria

After diagnosis within the first month of life, protein status was evaluated during the ensuing six months in infants with classical PKU who met the following criteria: full-term and appropriate-for-gestational-age and free of major congenital anomalies, cardiac, liver, neurological, renal, or pulmonary disease. Parents agreed to follow the nutrition-support protocol prescribed by the physician/nutritionist team at each study site.

Diet Assessment

Nutrient intakes, based on monthly 3-day diaries of amounts of foods ingested prior to each blood test, were calculated by

Amino Acid Analyzer® software (Ross Products Division). Since Phenex-1 contains L-amino acids, total nitrogen content $\times 6.25$ is used to describe its protein content. Mean intakes of medical food, protein, energy and twelve amino acids were used to estimate mean and standard error of the mean (SEM) intakes monthly and overall during the study. The percentages of the 1980 Recommended Dietary Allowances (RDAs) [5] for protein and energy supplied by the diet were determined.

Blood Collection and Analysis

Blood samples were drawn by venipuncture approximately two to four hours after feeding. Plasma was immediately separated from the erythrocytes and stored at -70°C until analysis; amino acids were analyzed at Ross Products Division, Abbott Laboratories by methods previously described [7]. Means (\pm SEM) and the percentage of amino acid concentrations, except Phe, falling below or above mean values (\pm SD $\times 2.13$) found for normal infants were calculated [7].

Plasma albumin and BUN concentrations were measured by automated procedures at each clinical site; transthyretin and RBP were analyzed by commercial enzyme immunoassay (Abbott Laboratories, North Chicago, Illinois). Means (\pm SEM) for the analytes were calculated and compared to reference ranges of 3.0 to 4.6 g/dL for albumin [8], 5 to 17 mg/dL for urea nitrogen [9], 6.7 to 21 mg/dL for transthyretin [10], and 1.0 to 7.6 mg/dL for RBP [10].

The decision was made to compare the data to normal reference data, given the small number of patients born yearly and the even smaller number of centers willing to cooperate in data collection. Many simple correlations were calculated *post hoc* using Pearson product moment correlations. Only those in which significant correlations ($p < 0.05$) were found are reported.

RESULTS

Subjects

Forty-two infants were enrolled, 31 in the in-depth study and 11 in a subgroup for whom only diet records, plasma amino acid concentrations and growth were evaluated. Four infants in the in-depth study and three in the subgroup were protocol failures and were not included in the data analyses. The remaining 35 infants (15 females and 20 males) were born at a mean gestational age of 38.7 (± 0.3 SEM) weeks. Thirty-three subjects were Caucasian. Subjects entered the study at 13.7 (± 1.9 SEM) days of age. Inadequate blood sample collection resulted in insufficient data for some infants at required times. Normal growth of these patients has been reported [11].

Table 1. Mean (\pm SEM) Medical Food, Protein, Energy and Selected Amino Acid Intakes by Infants by Month of Study and Overall During the Study

Variable	Month of Study						During Study
	1	2	3	4	5	6	
N	20	33	31	33	33	32	35
Medical Food (g/day)	61 (5)	61 (4)	69 (4)	83 (5)	93 (5)	97 (5)	79 (4)
Protein (g/day)	14.0 (0.7)	14.5 (0.6)	16.1 (0.6)	18.1 (0.7)	19.6 (0.7)	20.0 (0.7)	17.3 (0.6)
(g/kg/day)	3.2 (0.2)	2.8 (0.1)	2.6 (0.1)	2.6 (0.1)	2.6 (0.1)	2.4 (0.1)	2.7 (0.1)
Energy (kcal/day)	571 (23)	584 (20)	626 (22)	681 (24)	718 (26)	752 (24)	660 (18)
(kcal/kg/day)	132 (6)	111 (4)	102 (3)	98 (3)	94 (4)	92 (4)	103 (3)
Arginine (mg/day)	822 (50)	882 (44)	979 (42)	1122 (48)	1238 (51)	1287 (50)	1074 (40)
Cystine (mg/day)	158 (7)	161 (6)	170 (6)	193 (7)	204 (10)	219 (7)	186 (5)
Histidine (mg/day)	370 (20)	384 (18)	428 (18)	484 (20)	528 (21)	540 (20)	462 (16)
Isoleucine (mg/day)	914 (49)	934 (42)	1039 (44)	1178 (48)	1285 (52)	1315 (48)	1125 (39)
Leucine (mg/day)	1482 (78)	1524 (68)	1700 (70)	1915 (78)	2083 (83)	2122 (78)	1827 (63)
Lysine (mg/day)	952 (48)	981 (43)	1095 (44)	1225 (49)	1324 (53)	1331 (49)	1165 (40)
Methionine (mg/day)	296 (15)	309 (14)	346 (14)	385 (16)	416 (16)	421 (16)	367 (13)
Phenylalanine (mg/day)	221 (14)	250 (13)	270 (11)	264 (15)	265 (15)	254 (13)	255 (10)
Threonine (mg/day)	644 (32)	662 (28)	734 (29)	827 (32)	899 (36)	914 (32)	789 (26)
Tryptophan (mg/day)	183 (8)	189 (7)	205 (7)	228 (8)	244 (10)	244 (8)	218 (7)
Tyrosine (mg/day)	1144 (70)	1162 (60)	1300 (60)	1494 (68)	1640 (70)	1682 (69)	1423 (56)
Valine (mg/day)	1034 (57)	1055 (49)	1176 (51)	1333 (56)	1457 (59)	1492 (57)	1274 (46)

SEM = standard error of the mean.

Nutrient Intakes

Table 1 provides mean intakes (\pm SEM) of protein, energy, essential amino acids, arginine (Arg) and Cys. Seventeen percent of Phenex-fed infants had protein intakes below 100% of 1980 RDA; 80% of infants had energy intakes below 1980 RDA [3]. Mean intake of essential amino acids per kilogram of body weight were greater than recommended. Recommended Phe plus Tyr intake for normal infants is 141 mg/kg [3]. Overall mean (\pm SEM) Phe intake by infants in this study was 40 ± 1 mg/kg and Tyr intake was 219 ± 9 mg/kg [11].

Plasma Amino Acid Concentrations and Protein Status

Mean concentrations of plasma amino acids are given in Table 2. Mean concentrations of all amino acids except Cys, glycine (Gly) and Phe were in the reference ranges. A small percentage of some amino acids were below the lower limit of the reference range. These were Arg (12%), Cys (71%), isoleucine (Ile) (12%), lysine (Lys) (14%) and threonine (Thr) (11%). In the Phenex-fed infants, dietary intakes of Arg (month 3, $r = 0.36$, $p < 0.05$), methionine (Met) (month 4, $r = 0.43$, $p < 0.05$), Phe (months 1, 2 and 5, $r = 0.65$, $p < 0.01$; $r = 0.42$, $p < 0.05$; $r = 0.33$, $p < 0.07$), tryptophan (Trp) (month 1, $r = 0.51$, $p < 0.05$), Tyr (month 4, $r = 0.37$, $p < 0.05$) and valine (Val) (month 3, $r = 0.51$, $p < 0.01$) were positively correlated with the respective plasma amino acid concentrations. At one or more times during the study, aspartic and glutamic acids, Phe, and Tyr concentrations were positively correlated with the interval between last meal and blood

draw. Seventeen amino acid concentrations were negatively correlated with time from the last meal (Table 3).

At baseline, one (4%) of the infants in the present study had a plasma albumin concentration < 3.0 g/dL (Table 4). During the study, no subject had a plasma albumin concentration < 3.0 g/dL. All transthyretin concentrations were within the reference range (6.7 to 21 mg/dL) for infants between birth and five years of age [7,8]. RBP concentrations were all > 1.0 mg/dL and within the reference range (1.0 to 7.6 mg/dL) reported for one-to-five-year-old children [8]. During the study, no Phenex-fed infant had a low concentration of urea nitrogen.

DISCUSSION

Protein and Amino Acid Intakes

Analog-fed infants with PKU who weighed significantly less than infants in the present study [11,12] ingested, on average, 2.3 g/kg protein and 101 kcal/kg during the first six months of life [4], slightly lower than mean intakes of infants in this study. Infants, similar in mean weight to infants in the present study, fed Lofenalac[®], ingested significantly more protein and somewhat more energy, 3.6 ± 0.7 g (mean \pm SEM) protein/kg and 109 ± 20 kcal/kg [13], than present study infants. Analog-fed infants ingested a mean \pm SEM of 34 ± 2 mg Phe and 208 ± 12 mg Tyr per kilogram of body weight per day [4], while Lofenalac-fed infants ingested 48 ± 2 mg/kg of Phe [9], in contrast to 40 ± 1 mg Phe and 219 ± 9 mg Tyr by present study infants [11]. Intakes of all essential amino acids were greater than recommended.

Table 2. Mean (\pm SEM) Plasma Amino Acid Concentrations ($\mu\text{mol/L}$) of Infants by Month of Study and Overall during the Study

Variable	Reference Range [†]	Month of Study						During Study
		1	2	3	4	5	6	
N		20	33	31	33	33	32	35
Hrs postprandial blood drawn		2.40 (0.19)	3.03 (0.35)	2.45 (0.21)	2.80 (0.42)	2.64 (0.17)	2.70 (0.24)	2.68 (0.27)
Alanine	163–653	328 (21)	318 (21)	332 (26)	295 (14)	298 (12)	306 (16)	312 (18)
Arginine	51–132	102 (6)	84 (5)	80 (5)	76 (5)	78 (5)	77 (5)	82 (5)
Asparagine		36 (2)	36 (2)	32 (2)	32 (2)	29 (1)	29 (2)	32 (2)
Aspartic acid	3–44	12 (2)	12 (2)	10 (1)	9 (1)	8 (0)	8 (1)	10 (1)
Cystine	34–60	32 (3)	28 (2)	27 (2)	27 (2)	28 (2)	25 (2)	27 (2)
Glutamic acid	31–235	76 (7)	79 (7)	83 (8)	79 (6)	66 (5)	64 (4)	75 (6)
Glutamine	168–828	584 (20)	512 (17)	484 (14)	478 (12)	498 (19)	480 (11)	501 (15)
Glycine	104–297	306 (15)	278 (16)	252 (12)	234 (8)	246 (8)	250 (9)	258 (11)
Histidine	41–100	86 (4)	86 (2)	81 (4)	79 (2)	79 (3)	78 (2)	81 (3)
Isoleucine	49–103	86 (8)	84 (6)	87 (5)	81 (6)	80 (5)	85 (7)	84 (6)
Leucine	52–186	144 (12)	132 (9)	133 (7)	129 (8)	130 (7)	136 (10)	131 (9)
Lysine	120–254	198 (12)	183 (7)	168 (8)	161 (7)	162 (8)	158 (9)	170 (8)
Methionine	10–52	30 (2)	27 (2)	24 (1)	22 (1)	20 (1)	20 (1)	23 (1)
Phenylalanine	19–78	147 (40)	267 (46)	349 (42)	356 (44)	297 (35)	308 (36)	297 (41)
Proline	80–273	260 (18)	244 (11)	236 (14)	215 (13)	220 (13)	210 (15)	229 (14)
Serine	64–240	164 (7)	163 (14)	145 (5)	139 (4)	138 (4)	134 (4)	147 (6)
Taurine	17–152	94 (8)	86 (8)	92 (7)	90 (10)	84 (8)	81 (6)	88 (8)
Threonine	82–302	163 (8)	136 (9)	123 (8)	112 (6)	116 (6)	111 (6)	125 (7)
Tryptophan	22–90	52 (2)	49 (2)	52 (2)	53 (2)	51 (2)	54 (2)	52 (2)
Tyrosine	25–148	66 (10)	59 (4)	66 (6)	54 (4)	58 (6)	48 (3)	58 (5)
Valine	130–310	276 (17)	261 (14)	280 (12)	273 (12)	290 (10)	292 (14)	279 (13)

SEM = standard error of the mean; $\mu\text{mol/L}$ = micromoles per liter; Hrs = hours.

† Reference 5.

Plasma Amino Acid Concentrations and Protein Status

Plasma Cys concentrations were below the lower limit of the reference range in 71% of Phenex-fed and 94% of Analog-fed infants [4]. Low plasma Cys concentrations occurred in the present study despite intakes of Cys plus Met at more than two times the minimum intake recommended [3]. Binding of Cys in plasma that is not immediately deproteinized has been found in our laboratory and those of other investigators [14].

Plasma Phe concentrations of normal infants range from 19 to 78 $\mu\text{mol/L}$ [7]. Such low concentrations of plasma Phe in patients with PKU result in malnutrition, poor growth and mental retardation [2]. The range of plasma Phe concentration suggested for management of patients with PKU is 120 to 360 $\mu\text{mol/L}$. Although mean plasma Phe concentrations were within the treatment range in the present study, some 6% of samples had concentrations $<120 \mu\text{mol/L}$ and 37% had concentrations $>360 \mu\text{mol/L}$. Forty-four infants in the National PKU Collaborative Study [3], for whom the targeted plasma Phe concentration was 60 to 327 $\mu\text{mol/L}$, had a mean (\pm SEM) plasma Phe concentration of $326 \pm 163 \mu\text{mol/L}$ during the first six months of life. Substantial difficulty occurred in maintaining plasma Phe concentration in the target range. Analog-fed infants had a mean plasma Phe concentration of $310 \pm 81 \mu\text{mol/L}$ [4]. Inappropriate diet prescription, rapidly changing

Phe requirement, illness of the subject or poor parental compliance may each have contributed to plasma Phe concentrations greater than 360 $\mu\text{mol/L}$.

Buist et al. [15] reported that, except for Gly, all mean fasting plasma amino acid concentrations of children who were fed Periflex[®] (Scientific Hospital Supplies, Ltd, Gaithersburg, Maryland) or Phenyl-Free[®] (Mead Johnson Nutritionals, Evansville, Indiana) were lower than those found in normal children. Low mean fasting concentrations of amino acids found by Buist et al. [15] contrast sharply with the normal mean concentrations found for most amino acids in the present study where blood was drawn two to four hours after feeding. Twenty-three percent of plasma Gly concentrations were elevated in infants in the present study, compared to 62% in Analog-fed infants [4]. Analog XP contains 69 mg Gly/g protein and Phenex-1 contains 67 mg Gly/g protein. Several groups of investigators [15–17] found elevated plasma Gly concentrations in patients with PKU who were undergoing therapy. Periflex fed by Buist, et al. [15] contains no Gly. According to Arroyave [18], elevated plasma Gly concentrations are indicative of protein malnutrition. Analog-fed infants ingested significantly less protein per day than Phenex-fed infants [4].

Our data strongly suggest that the timing of blood sampling had a greater effect on most plasma amino acid concentrations than the amounts of L-amino acids fed to infants. The time

Table 3. Pearson's Correlation Coefficients between Hours Postprandial Blood was Drawn and Plasma Amino Acid Concentrations

	Month of Study					
	1	2	3	4	5	6
No	20	30	31	32	31	29
Vs Plasma Amino Acid Concentration						
Alanine	NS	NS	$r = -0.46; p < 0.05$	NS	NS	NS
Arginine	NS	$r = -0.46; p < 0.05$	$r = -0.48; p < 0.01$	NS	NS	NS
Asparagine	NS	NS	$r = -0.40; p < 0.05$	NS	NS	NS
Aspartic Acid	NS	$r = 0.69; p < 0.001$	NS	NS	NS	NS
Cystine	NS	NS	NS	NS	NS	$r = -0.35; p < 0.06$
Glutamic Acid	NS	$r = 0.60; p < 0.001$	NS	NS	NS	NS
Glutamine	NS	NS	$r = -0.44; p < 0.01$	NS	NS	NS
Glycine	NS	NS	$r = -0.52; p < 0.01$	NS	NS	NS
Histidine	NS	NS	NS	NS	NS	$r = -0.42; p < 0.05$
Isoleucine	NS	NS	$r = -0.53; p < 0.01$	$r = -0.44; p < 0.05$	NS	NS
Leucine	NS	NS	$r = -0.50; p < 0.01$	$r = -0.42; p < 0.05$	NS	NS
Lysine	NS	NS	$r = -0.40; p < 0.05$	NS	NS	NS
Methionine	NS	NS	$r = -0.61; p < 0.001$	NS	NS	NS
Phenylalanine	NS	NS	$r = 0.51; p < 0.01$	NS	NS	NS
Proline	NS	NS	$r = -0.45; p < 0.05$	NS	NS	NS
Serine	NS	NS	$r = -0.57; p < 0.001$	NS	NS	NS
Threonine	NS	NS	$r = -0.66; p < 0.001$	NS	NS	NS
Tryptophan	NS	NS	$r = -0.37; p < 0.05$	NS	NS	NS
Tyrosine	$r = 0.43; p < 0.05$	NS	NS	NS	NS	NS
Valine	NS	NS	$r = -0.40; p < 0.05$	$r = -0.45; p < 0.05$	NS	NS

NS = Not significant.

Table 4. Mean (\pm SEM) Indices of Protein Status of Infants by Month of Study and Overall

Variable	Baseline	Month of Study			During Study
		1	3	6	
Albumin, g/dL	3.7 (0.1) [22]	3.6 (0.1) [24]	4.1 (0.1) [23]	4.1 (0.1) [26]	3.9 (0.1)
Retinol binding protein, mg/dL	NE	NE	3.38 (0.2) [22]	3.74 (0.2) [21]	3.56 (0.2)
Transthyretin, mg/dL	NE	NE	17.6 (0.8) [22]	17.9 (0.9) [22]	17.8 (0.8)
Urea nitrogen, mg/dL	12.9 (1.2) [23]	12.3 (0.8) [23]	12.0 (0.6) [24]	11.9 (0.5) [24]	12.1 (0.6)

(SEM) = standard error of the mean.

[] = No. of patients.

NE = Not evaluated.

elapsed between meal and blood draw in the present study ranged from 2.40 to 3.03 hours. According to Gropper, et al. [19] plasma amino acid concentrations in normal adult males peaked at 30 minutes after a meal in which 75% of protein was derived from synthetic L-amino acids and 25% from intact protein, in contrast to the peak found at 150 minutes after a meal of intact protein [19].

Mean daily total Tyr intakes of infants fed Phenex were greater than intakes of infants fed Analog [4]. Analog-fed infants, however, had higher mean plasma Tyr concentrations. Reasons for lower, but normal mean plasma Tyr concentrations in infants fed Phenex are unclear, but may be related to competition between branched chain amino acids and Tyr for the same intestinal transport system [20], better growth by the Phenex-fed infants [11,12] and the time after feeding blood was

drawn [19]. Van Spronsen et al. [21] reported large fluctuations in plasma Tyr concentrations of treated patients with PKU.

Shenton et al. [3] has previously reported lower than normal plasma transthyretin concentrations in children with PKU and suggested that the low values were indicative of marginal malnutrition. Trp, known to exert a key role in the polyribosomal aggregation required for liver protein synthesis [22], was adequate in the diets of infants in the present study, and all had normal plasma Trp concentrations. Although no correlation was found between transthyretin concentrations and energy, protein or amino acid intakes in this study, plasma concentrations of Met ($r = 0.59; p < 0.01$), serine ($r = 0.57, p < 0.01$) and Thr ($r = 0.57, p < 0.01$) were positively correlated with plasma transthyretin concentrations. In the present study, mean plasma concentrations of transthyretin were slightly greater

than those found in 3.7 month old infants fed a soy protein isolate formula from birth [23].

CONCLUSIONS

Phenex-1, as fed to infants in the study, maintained protein status indices in the reference ranges. This study supports the recommendation of the Medical Research Council Working Party on Phenylketonuria [24] for 3 g/kg/day of amino acids from medical food for infants.

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