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Research Communications

Adequacy of sulfur amino acid intake in infants receiving parenteral nutrition

Richard A. Helms,*†‡ Michael L. Christensen,*‡ Michael C. Storm,§ and Russell W. Chesney†‡

**Department of Clinical Pharmacy and †Pediatrics, ‡The Center for Pediatric Pharmacokinetics and Therapeutics, The University of Tennessee, Memphis, TN USA; §Nutrition Research, McGaw, Inc., Irvine, CA USA*

Taurine and cysteine are considered essential nutrients for the infant receiving parenteral nutrition (PN). To define the adequacy of sulfur amino acid content in a pediatric amino acid formulation, evaluation of urinary excretion, fractional excretion, and balance studies for taurine, total (free + bound) cyst(e)ine (cysteine + cystine), and methionine were completed under steady-state conditions of energy and protein intake in 18 preterm infants receiving PN. These infants had a mean gestational age of 34.5 ± 2.4 weeks, postnatal age of 19 ± 18 days, weighed 2.1 ± 0.5 kg, and received 100 ± 22 kcal/kg/day and 2.8 ± 0.1 g/kg/day of amino acids. Plasma concentrations for the sulfur-containing amino acids were within the reference range; however, the excretion and fractional excretion of taurine (3.7 ± 7.8 mg/kg/day, 17 ± 15%) and cyst(e)ine (12.0 ± 7.1 mg/kg/day, 33 ± 19%) were at the upper limits of normal reported experience. Methionine excretion (0.9 ± 1.0 mg/kg/day) and fractional excretion (16 ± 22%) were within normal reported experience. For taurine, fractional excretion inversely correlated with weight at the time of study ($r = -0.59$, $P < 0.001$), while for total cyst(e)ine and methionine, no correlation could be found for gestational age, postconceptional age, or weight. Taurine excretion may be a result of varying renal maturity in the study infants, and dosing may need to be adjusted based on renal maturity. Excessive dosing may explain cysteine excretion, while methionine excretion and fractional excretion suggest appropriate dosing. (J. Nutr. Biochem. 6:462–466, 1995.)

Keywords: parenteral nutrition; infants; amino acids; sulfur

Introduction

The sulfur amino acids are important in infant nutrition. Cysteine is a component of proteins, important for secondary structure, and also a precursor for glutathione. Taurine appears to have a central role in biological functions including bile acid conjugation, cell membrane stabilization, antioxidation, detoxification, osmoregulation, neuromodulation, and brain and retinal development.[1] Preterm and newborn infants have a functional immaturity in the transsulfuration pathway leading to an impairment in the metabolism of sulfur-containing amino acids.[2] Hepatic γ-cystathionase and cysteinesulfinic acid decarboxylase enzyme activity is either absent or very low, resulting in dietary requirement for cysteine and taurine.[3–5] Unlike the other sulfur-containing amino acids, the pool size for taurine is regulated by the kidney, with the exception of renal immaturity.[1] Decreased plasma and urine taurine concentrations in preterm infants fed formulas devoid of taurine compared with breast-fed infants have led to taurine supplementation of most infant formulas to levels similar to that found in breast milk.[1] Significantly lower taurine values have been observed in premature infants maintained on taurine-free parenteral nutrition (PN) when compared with infants fed taurine-containing formula.[6] Similarly, low total

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Address reprint requests to Richard A. Helms, Department of Clinical Pharmacy, 26 South Dunlap, Memphis, TN 38163, USA.
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cyst(e)ine (cysteine + cystine) concentrations have been reported in infants receiving PN containing minimal amounts of cysteine.[7,8] These observations led to the development of pediatric amino acid formulations that contain taurine with cysteine being added to PN solutions immediately prior to administration.

The quantity of methionine, taurine, and cysteine admixture in the pediatric amino acid formulation (TrophAmine, McGaw, Inc., Irvine, CA) was established through multiple regression analyses relating the plasma concentration to intake for a wide variety of standard amino acid formulations.[9] The target concentration for each amino acid was derived from healthy, normally growing 1-month-old breast-fed term infants.[10] This range has been suggested as a better plasma amino acid target range than that obtained from either cord or fetal blood.[11] Clinical testing in a small number of infants led to formulation adjustment and further clinical testing.[9,12] This pediatric amino acid formulation has been associated with improved weight gain and nitrogen retention in infants receiving PN.[13]

We have re-evaluated the adequacy of the sulfur amino acid content of this pediatric amino acid formulation by measuring the urinary excretion, balance and retention of taurine, total cyst(e)ine, and methionine in postsurgical infants.

Methods and materials

Postsurgical infants without liver or kidney dysfunction and not receiving drugs known to affect amino acid metabolism who required PN were studied following informed consent. Enrollment criteria included a gestational age greater than 28 weeks, a postnatal age less than 2 months, no oral intake on entrance into the study, and receiving at least 2.5 g/kg/day of amino acids as TrophAmine and greater than 60 kcal/kg/day. L-cysteine · HCl · H_2O was admixed at 40 mg/g of amino acids. This is the equivalent of 28 mg of cysteine/g of amino acids. Lipids, electrolytes, and trace elements were provided in quantities estimated to meet daily requirements. The infusion rate of the PN solution was controlled by a volumetric infusion pump accurate to less than ±4%.

Blood samples and 24 hr acidified urine samples for the quantitation of taurine, total cyst(e)ine, and methionine were obtained under steady-state conditions after 3 to 5 days of PN administration and at least 48 hr following changes in parenteral solution delivery rates or administration of blood products. Serial collections (every 5 to 7 days) were made on patients remaining on PN greater than 10 days. All blood samples were collected between 0700 and 0900 hr, and the plasma was immediately separated and a portion was deproteinized with 5′-sulfosalicylic acid at 40 mg/mL of plasma and stored at −70°C until analysis. The whole plasma was used to measure total (free + bound) cyst(e)ine after dithiothreitol treatment. Twenty-four hour acidified urine collections were maintained at 4°C until the collection was complete. All urine had to be accounted for through the use of tared diapers and urine bags. Eighty percent of the urine produced in 24 hr had to be collected for a valid collection. After thorough mixing and recording the total volume, an aliquot was stored at −70°C until analysis.

Plasma and urine taurine and methionine concentrations were determined on a Beckman 6300 Amino Acid Analyzer using a 10 cm Li High Performance Column and a four buffer (lithium citrate) expanded physiologic program (Beckman Instruments, Inc., Palo Alto, CA). Total cyst(e)ine was determined in whole plasma and urine samples by the spectrophotometric method of Gaitonde as modified by Malloy, et al.[14,15] Both cysteine · HCl · H_2O (Ajinomoto Co., Inc., Raleigh, NC USA) and D-glucose-L-cysteine (Sigma Chemical Co., St. Louis, MO USA) were run as standards.

The amount of each amino acid excreted in a 24 hr period was calculated by multiplying the urinary amino acid concentration by the total 24 hr urine volume and dividing this product by the patient's weight. The fractional excretion for each amino acid was calculated by the following formula:

$$\frac{U_{aa}}{U_{cr}} \times \frac{P_{cr}}{P_{aa}} \times 100\%$$

where U = urine concentration, P = plasma concentration, aa = amino acid, and cr = creatinine. Estimation of amino acid balance was calculated by subtracting the amount of amino acid excreted in the urine in the 24 hr period from the intake of that amino acid. The retention (%) of each amino acid was calculated by dividing the amino acid balance by the intake multiplied by 100. Relationships were assessed using simple linear regression analysis. Results are presented as mean and standard deviation.

Results

A total of 18 infants, gestational age 34.5 ± 2.4 weeks, postnatal age 19 ± 18 days, and weighing 2.1 ± 0.5 kg were studied (*Table 1*). These infants received a mean of 100 ± 22 kcal/kg/day and 2.8 ± 0.1 g/kg/day of amino acids at the time of study. There were a total of 32 observations made in these 18 infants (8 infants–1 observation, 7 infants–2, 2 infants–3, and 1 infant–4). Multiple observations made in the same infant were separated by 7 days and treated as independent samples for the purpose of regression analysis of excretion versus age or weight. To avoid possible bias because multiple observations were made more commonly in smaller infants, mean subject data were used for univariant analyses. The plasma concentrations of taurine, total cyst(e)ine, and methionine are summarized in *Table 2*. The mean plasma concentrations of the three sulfur-containing amino acids were within the 95% confidence limits of the reference range.[10] The reference range for total cyst(e)ine was determined on whole plasma using the identical reduction process.

A standard curve for the modified Gaitonde assay based on cysteine · HCl · H_2O produced a molar extinction coefficient of 14.3×10^3 L/mol/cm similar to the originally observed value.[14] A standard curve based on D-glucose-L-cysteine in this assay produced a molar extinction coeffi-tk;1 cient of 10.9×10^3 L/mol/cm indicating a somewhat reduced sensitivity for this compound. Final reaction products yielded similar UV-visible absorption spectra (data not shown). Since it is not possible with this analytical technique to differentiate between cysteine and D-glucose-L-cysteine in samples, the assay results have been interpreted as reflecting total cysteine/cystine concentrations.

Intake, excretion, balance, and retention for taurine, total cyst(e)ine, and methionine are summarized in *Table 3*. Methionine is avidly retained (99%). Lack of renal conservation is evident for both taurine and total cyst(e)ine. Eight

Table 1 Patient characteristics

Patient	Sex	Age (days)	Gestational age (weeks)	Weight (kg)	Diagnosis*	Protein intake (gm/kg/day)	Caloric intake (kcal/kg/day)	Number observations
1	M	4	34	1.87	AWD	2.72	124	4
2	M	55	39	2.96	NEC	2.97	124	1
3	F	33	32	1.28	NEC	2.99	116	1
4	M	13	32	1.11	AWD	2.68	80	3
5	M	6	35	1.89	NEC	2.68	100	2
6	F	18	37	2.34	NEC	2.88	107	1
7	F	7	37	2.44	AWD	2.73	117	3
8	M	19	35	1.39	NEC	2.68	150	2
9	F	40	37	2.38	NEC	2.78	63	1
10	M	64	32	2.38	AWD	2.69	83	1
11	M	26	34	2.43	AWD	2.80	75	2
12	M	9	38	2.94	AWD	2.76	87	2
13	F	5	34	1.91	AWD	2.62	107	2
14	F	6	34	2.06	AWD	2.94	112	1
15	F	6	31	1.74	AWD	2.69	73	1
16	M	21	31	1.92	NEC	2.74	90	2
17	M	3	35	2.80	NEC	2.71	108	2
18	F	2	34	2.38	AWD	2.82	88	1

*AWD, abdominal wall defect, NEC, necrotizing enterocolitis

of 32 observations had taurine retentions <50% and in 7 of 32 observations there were negative taurine balances; these were found in subjects 1, 3, 4, 5, and 8, five of our six smallest infants on entrance into the study. Fractional excretion of taurine was greater than 20%, the upper limits of normal[6,16] for 11 observations in the aforementioned infants plus subject 15. Therefore, negative taurine balance, taurine retention <50% and taurine fractional excretion >20% were only observed in the six smallest study subjects. The fractional excretion of taurine inversely correlated with weight (*Figure 1*). Other demographic parameters including postconceptional age, postnatal age, and gestational age also inversely correlated with fractional excretion of taurine, but less strongly than did weight. By contrast, neither cyst(e)ine fractional excretion nor excretion correlated with any patient demographic parameter. Total cyst(e)ine excretion was near the upper limits reported in preterm infants fed human milk.[8]

Discussion

Our findings suggest that the pediatric formulation has adequate content of methionine, cysteine, and taurine for this postsurgical population of infants, whenever amino acid intake is in the range of 2.5 to 3.0 g/kg/day and nonprotein calories exceed 60 kcal/kg/day. Although renal wasting of taurine is substantial, steady-state plasma concentrations are similar to those of breast-fed infants; indeed balances were generally positive. Mean total cyst(e)ine plasma concentrations were 1.73 SD above the reference range and excretion at the upper limits of normal suggesting that a reduction in cysteine · HCl · H_2O dose might be evaluated. This finding and the suggestion on dosing adjustment are complicated by our inability to distinguish cysteine from D-glucose-L-cysteine in plasma or urine, an issue we will return to later in the discussion. Potential changes in cysteine intake would necessitate global assessment of sulfur amino acid nutrition, since this may influence methionine and taurine requirement in parenteral amino acids solutions.

Cysteine is thought to be an essential nutrient because of enzyme immaturity in the transsulfuration pathway.[2–5] Sturman found that not only was cystathionase activity nearly absent from fetal hepatic tissue extracts, but that cystathionine synthase and methionine activating enzyme activities were at 20 to 30% of adult values.[3] Low total cyst(e)ine plasma concentrations has been reported in infants given PN that contains methionine but minimal amounts of cysteine.[7,8] Further, Synderman found that the absence of oral cysteine intake in premature infants resulted in a fall in plasma cystine values, decrease in weight gain, and decrease in nitrogen retention.[17] Low total cyst(e)ine plasma values have also been observed in adults given a methionine-rich, cysteine-free parenteral formula.[18,19] When the same parenteral formula was administered enterally to these adults, normal plasma total cyst(e)ine values were maintained. These findings demonstrate the potentially important effect of route of administration on the ability of the liver to synthesize cysteine. Zlotkin confirmed low hepatic cystathionase activity in preterm and full-term infants but he was unable to show enhanced weight gain or nitrogen re-

Table 2 Plasma taurine, cyst(e)ine, and methionine concentrations

Amino Acid	Plasma concentration (μmol/dL)	Reference concentration* (μmol/dL)	Z score†
Taurine	7.0 ± 3.3	8.4 ± 3.9	−0.36
Total cyst(e)ine	19.8 ± 6.4	15.3 ± 2.6	1.73
Methionine	4.0 ± 2.0	3.6 ± 0.7	0.57

*From Wu.[10]
†Z score = plasma concentration − reference concentration/standard deviation reference concentration

Table 3 Intake, excretion, balance, and retention of taurine, cyst(e)ine, and methionine

Amino Acid	Intake (mg/kg/day)	Excretion (mg/kg/day)	Fractional excretion (%)	Balance (mg/kg/day)	Retention (%)
Taurine	6.5 ± 0.6	3.7 ± 7.8	17 ± 15	2.8 ± 7.7	43 ± 116
Cysteine	77.4 ± 7.0	—	—	—	—
Total cyst(e)ine	—	12.0 ± 7.1	33 ± 19	66.0 ± 7.2	86 ± 8
Methionine	87.8 ± 7.9	0.9 ± 1.0	16 ± 22	87.5 ± 6.1	99 ± 1

tention with cysteine supplementation.[20,21] This may have been due to limiting concentrations of other amino acids such as tyrosine.[22] The estimated cysteine requirements for preterm infants from parenteral or enteral intake is 80 to 85 mg/kg/day (~0.70 mmol/kg/day).[8,17] Infants in the current study had cysteine intakes similar to these recommended amounts, 77 mg/kg/day (0.64 mmol/kg/day).

There is limited data on normal ranges for the excretion of total cyst(e)ine because of methodologic problems in quantitating cyst(e)ine. The excretion of total cyst(e)ine was at the upper limits reported in human milk–fed preterm infants[16] and similar to values reported by Heird et al. in parenterally fed infants with a similar cysteine intake.[12] The absence of correlation between total cyst(e)ine fractional excretion or excretion and any demographic parameter suggests renal mechanisms for total cyst(e)ine conservation are not developmentally linked as they are for taurine.

D-glucose-L-cysteine, the thiazolidine adduct of D-glucose and L-cysteine, has been reported to occur in TPN solutions containing concentrated D-glucose and added L-cysteine · HCl · H_2O.[23] Indeed this compound does produce a ninhydrin positive peak on our amino acid analysis system with a retention time of approximately 3.4 min. A small peak with similar retention time also appears during the amino acid analysis of TPN solutions containing added cysteine and does not appear during the analysis of TPN solutions without added cysteine. Unfortunately, during the analysis of physiological samples, this peak appears to coelute with phosphoethanolamine. We have not been able to differentiate these peaks and cannot delineate the relative contribution of D-glucose-L-cysteine in plasma or urine samples. While it has been reported that 50 to 60% of added cysteine is complexed as D-glucose-L-cysteine, recent studies suggest that D-glucose-L-cysteine is a bioavailable form of cysteine[24,25] making assessment of excretion and estimation of retention and balance possible. In order to recommend with confidence the ideal dose of L-cysteine · HCl · H_2O, analytical procedures are necessary to distinguish cysteine from its adduct in biologic fluids.

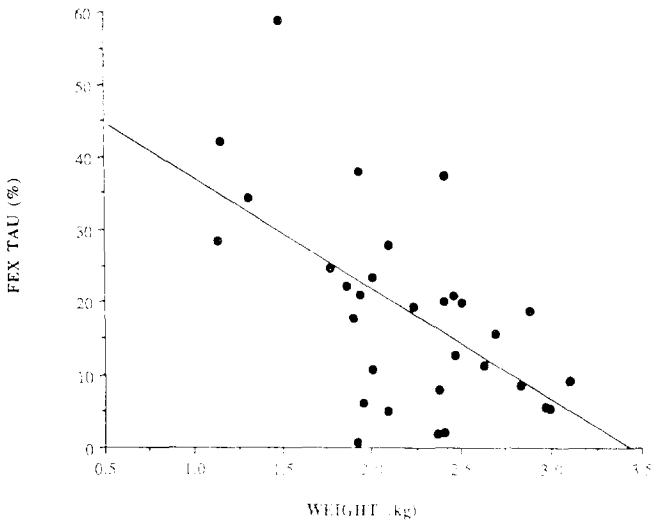

Figure 1 Relationship between weight and the fractional excretion of taurine (FEX TAU). $r = -0.59$. $P < 0.001$

Until the introduction of pediatric-specific amino acid formulations, parenteral amino acid formulations did not contain taurine. We observed normal plasma taurine concentrations in infants receiving a pediatric amino acid formulation that contains taurine. The mean taurine fractional excretion was at the upper end of normal. Under normal conditions in human adults, the fractional excretion of taurine is 5 to 10% and may be as high as 20% in the normal infant.[6] Premature infants may have marked increases in taurine fractional excretion that likely reflects the immaturity of the renal tubular transport system and the inability of the nephron to reabsorb fully taurine despite hypotaurinemia.[6,22,26] We also found taurine fractional excretion to correlate inversely with weight and is consistent with the maturational changes of the renal tubule.[27] Because of these maturational differences in taurine retention, it is difficult to speculate on ideal taurine content in parenteral feedings. The age and size of the patient, content of other sulfur-containing amino acids, and total protein intake are likely to affect taurine dosing. For this postsurgical population of infants, taurine intake appears adequate, but may not meet the need of the very-low-birth-weight infant where renal wasting may be more significant.

Several assumptions are necessary for the calculations of amino acid balance and retention. These include little or no conversion of methionine to cysteine and cysteine to taurine via the trans-sulfuration pathway, and since all infants were in positive nitrogen balance at the time they were studied (data not shown), there was minimal net contribution to the sulfur amino acid pool from protein turnover. Arguably, since some infants were more mature than others, there may have been trans-sulfuration pathway activity in these infants. Zoltkin, however, found very limited hepatic γ-cystathionase activity at birth in term infants; this activity did not reach adult values until 60 to 90 days postnatal age or 340 to 370 days postconceptional age.[21] Hepatic γ-cys-

tathionase did not reach peak activity (1.7 times adult activity) until greater than 120 days postnatal age. All of our infants were less than 300 days postconceptional age, except for infant 2 who was nearly 330 days postconceptional age.

In summary, for postsurgical infants, there appears to be adequate quantities of methionine, cysteine, and taurine in the tested pediatric amino acid formulation. A reduction in cysteine · HCl · H_2O admixture might be evaluated, more specific analytical procedures should be developed, and formulation alternatives need to be considered.[28] Adequacy of taurine intake for the very-low-birth-weight neonate has not been assessed by this investigation, but data suggest that dosing adjustments may be required due to renal wasting.

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