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Parenteral Nutrition–Associated Cholestasis in Neonates: Multivariate Analysis of the Potential Protective Effect of Taurine

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ABSTRACT. *Background:* Neonates receiving parenteral nutrition (PN) are at risk for PN-associated cholestasis (PNAC); however, no preventive factors for PNAC have been clearly identified. Despite reports suggesting that taurine may prevent PNAC in neonates, such an effect of taurine has not yet been definitively demonstrated. We determined whether taurine supplementation reduces the incidence of PNAC in premature or critically ill neonates. *Methods:* This study was part of a prospective, randomized, multi-institutional trial designed to assess cholecystokinin *vs* placebo as a potential preventive therapy of PNAC. Taurine supplementation of PN varied between institutions. The presence or absence of taurine in PN was analyzed by multivariate analysis, with a primary outcome measure of serum conjugated bilirubin (CB) as a measure of PNAC. *Results:* Taurine reduced PNAC in premature infants (estimated maximum CB [95% confidence interval] 0.50 mg/dL [−0.17 to 1.18] for those receiving taurine, *vs* 3.45 mg/dL [1.79–5.11] for neonates not receiving taurine, approaching significance, $p = .07$). Taurine significantly reduced PNAC in infants with necrotizing enterocolitis (NEC; estimated maximum CB 4.04 mg/dL [2.85–5.23], NEC infants receiving taurine, *vs* 8.29 mg/dL [5.61–10.96], NEC infants not receiving taurine, $p < .01$). There were too few neonates with surgical anomalies to evaluate the effect of taurine in this group. *Conclusions:* Within specific subgroups of neonatal patients, taurine supplementation does offer a very significant degree of protection against PNAC. Patients with NEC or severe prematurity are most likely to benefit substantially from taurine supplementation. (*Journal of Parenteral and Enteral Nutrition* **29:**337–344, 2005)

Since the landmark 1968 report by Wilmore and Dudrick[1] of the first neonate sustained by receiving parenteral nutrition (PN), experience with PN has come a long way. Unfortunately, PN-associated cholestasis (PNAC) remains a significant problem not only in terms of incidence but also in lack of effective treatment and the morbidity and mortality associated with this process. Recently, the incidence of neonatal PNAC has been reported at 25%,[2] and the associated mortality may range from 20% to 31%.[2,3] Risk factors for PNAC include sepsis and prematurity.[4] But prevention of PNAC remains an elusive goal, especially in the neonate. Suggested measures to prevent PNAC have ranged from cycling of PN[5] to prevention of sepsis[4] and administration of bile salts,[6] cholecystokinin,[7] or metronidazole.[8] However, no preventive measure has been uniformly successful.

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Over 20 years ago, Cooper et al reported marked deficiency of taurine in 3 children with severe PNAC.[9] Although a flurry of subsequent animal studies found that supplemental taurine increased tauroconjugated bile acids in rats[10] and enhanced bile flow and bile acid secretion in guinea pigs,[11] the effect of taurine on PNAC in humans remained unknown. What became clear, however, was that children receiving long-term PN not only develop taurine deficiency[12,13] but that taurine levels may subsequently be corrected by addition of taurine to PN solutions.[14,15] One study attempted to determine whether taurine supplementation in PN could prevent PNAC, but this study was significantly underpowered (only 20 patients), and its duration was too short—only 10 days—to detect an effect of taurine.[16] As most episodes of PNAC occur after 2 weeks of PN,[3,7,17] a longer study period was needed. Thus, whether taurine supplementation is preventive of PNAC in human neonates has remained an unproven hypothesis.

We therefore sought to determine whether a preventive effect of taurine supplementation could be found in a large population of very premature or acutely ill neonates receiving PN, with or without taurine. Our

hypothesis was that taurine would decrease cholestasis and possibly reduce some of the attendant morbidity and mortality of PNAC.

MATERIALS AND METHODS

Study Design

This study was conducted prospectively between 1996 and 2001 at 7 participating institutions. The purpose of the study was to examine the effect of cholecystokinin-octapeptide (CCK) on the development of PNAC in neonates. Because the use of taurine supplementation varied between the study institutions (initially, some of the institutions used PN containing taurine and some did not), the decision was made *a priori* to additionally examine the effect of taurine supplementation on the development of PNAC. Therefore, subjects were randomized to receive either CCK or placebo in a double-blind fashion, but the presence or absence of taurine in the PN was not controlled by the investigators. The decision regarding PN formula of choice was dictated by local practice and hospital formularies. An analysis of the effect of CCK on PNAC has been performed and will be published separately.[18] CCK was not found to be efficacious in the prevention of PNAC. However, the study design allowed us to examine the effect of taurine on the development of PNAC. By the end of the study period, all institutions involved had acquired taurine-containing PN formulations for neonatal use. The study was funded by the Food and Drug Administration Orphan Products Grant Program and was assigned IND 42,898. Full institutional review board approval was obtained from each participating institution, and informed written consent was obtained from the parents or legal guardian of every subject enrolled.

Study Population

Each center participating in this study is a tertiary care facility for neonates with a large regional referral pattern exceeding 10,000 live births per year. Homogeneity of data collection and standardization of definitions was established by meetings between coinvestigators and study coordinators with the principal investigator (DHT) and maintained by study coordinators at each site. The total number of patients enrolled was 243, of which 236 could be used in analysis.

Rationale for Choice of Variables

PNAC has been variously defined, but the diagnosis essentially requires an elevation in conjugated bilirubin (CB) in patients receiving PN, in the absence of an alternative cause for hyperbilirubinemia.[2–7] Therefore, CB was chosen as the primary outcome variable; patients with non–PN-related elevations in CB were excluded, as described in detail below.

Secondary outcome variables examined were the incidence of sepsis, mortality rate, length of time to achieve 50% and 100% of caloric intake *via* the enteral route, and the number of intensive care unit days and hospital days. Although none of these variables defines PNAC, development of PNAC may influence each of these variables. Thus, a reduction in PNAC might be anticipated to correlate with a reduction in mortality, sepsis, or duration of PN. In addition, baseline characteristics included in the analysis were gestational age, birth weight, and diagnosis.

Inclusion Criteria

All patients had to require >50% of caloric intake by the parenteral route. Initially, only severely premature infants were recruited into the study (defined as <1000 g birth weight and with an estimated [Dubowitz] gestational age ≤28 weeks). However, because the majority of these patients were found to achieve >50% of caloric intake enterally by 7–14 days, the inclusion criteria were expanded to include neonates <30 days of age (at the time of enrollment) who had necrotizing enterocolitis (NEC) meeting or exceeding Bell grade II[19] or a surgical indication for prolonged PN. Surgical indications comprised 2 subsets of patients: gastroschisis and severe jejunoileal atresia (with a loss of at least 50% of the anticipated small-bowel length for a given gestational age).[20] All patients were recruited into the study protocol within seven days of the diagnosis of any one of these disorders. Patients with hemodynamic instability (see below) were recruited but not begun on the study until hemodynamically stable, and then only if still <30 days of age.

Exclusion Criteria

Exclusion criteria, with the exception of hemodynamic instability, were applied before enrollment. Hemodynamically unstable patients could enroll but not begin the study protocol until achieving hemodynamic stability within 30 days of life (instability defined as fluid bolus requirements exceeding 40 mL/kg in the previous 24 hours in addition to maintenance fluids; or requirement for adrenergic support >10 μg/kg/min of either dopamine or dobutamine, or ≥0.1 μg/kg/min of epinephrine). Absolute exclusion criteria included all non-PN causes of cholestasis. Therefore, patients were excluded if diagnosed with any metabolic pathway defect (including hereditary fructose intolerance, galactosemia due to transferase deficiency, and neonatal tyrosinemia), primary or secondary liver disease, or progressive renal failure (defined as creatinine >1.5 mg/dL). Additionally, patients underwent an initial hepatobiliary ultrasound to exclude any neonate with suspected congenital obstruction of the hepatobiliary tree (eg, biliary atresia or choledochal cyst). Further exclusion criteria were extracorporeal life support or a diagnosis of HIV infection. No patient was enrolled beyond the times listed in the inclusion criteria, and no patient was enrolled if the CB was >1.0 mg/dL. Finally, infants were excluded if they had received ursodeoxycholic acid before the study, and no patient received this drug while participating in the study.

PN Administration

To insure the uniform delivery of PN between patients and sites, PN was administered according to

standardized guidelines, as follows. Total nonprotein caloric delivery did not exceed 90–100 kcal/kg/d. Carbohydrate administration was begun at 4–8 mg/kg/min on the first day of PN and advanced to 11–18 mg/kg/min by the third day. Provision was given for patients who were glucose intolerant during this advancement; that is, the protocol allowed clinicians to reduce carbohydrate infusion or administer insulin as needed. Protein administration was begun at 1.0 g/kg/d on the first day of PN and advanced by 0.5–1.0 g/kg/d to a maximum of 3.0 g/kg/d. Lipid administration began at 1.0 g/kg/d on the first day of PN and was advanced by 0.5–1.0 g/kg/d to a maximum of 3.0 g/kg/d. The presence or absence of taurine in each formulation was recorded. A pediatric amino acid formulation that contained taurine was used for those patients receiving taurine-supplemented PN. This was either Aminosyn-PF ($n = 73$) (Abbott, Abbott Park, IL; 10% solution containing 70 mg/100 mL in the bulk solution), or else Trophamine ($n = 122$) (B. Braun, Bethlehem, PA; 10% solution containing 25 mg/100 mL in the bulk solution). The dose of taurine was dependent on total protein delivery and formulation and ranged from 6.0 to 21.6 mg/kg/d. For those neonates in which taurine was not included in the formulation, a standard adult formulation was used ($n = 41$, Aminosyn, Abbott).

Measurements and Definitions

The primary outcome, serum CB levels, was measured within 72 hours before, or on, the day of recruitment into the study and weekly thereafter. All sample measurements of CB were performed using a Kodak Ektachem 750 system (currently Johnson & Johnson Inc, USA).

Secondary outcome measures included the incidence of sepsis, mortality rate, length of time to achieve 50% and 100% of caloric intake *via* the enteral route, and number of intensive care unit days and hospital days. The definition of sepsis included both generalized and catheter-related sepsis and was based on previously established definitions.[21] Catheter sepsis was defined using a modified definition established by the Centers for Disease Control and Prevention.[22] Percent of calories taken enterally was calculated by dividing the number of calories delivered enterally by the total number of calories delivered (enteral plus parenteral, inclusive of all protein sources) per day. To reach the definition of achieving 50% or 100% of calories by the enteral route, infants had to tolerate this level of feeding for 3 consecutive days. Mortality was defined as a death occurring at any time during the child's admission to the hospital.

Statistical Analysis

Baseline characteristics (gestational age and birth weight) of the 2 groups (with or without taurine) were first compared with a 2-tailed unpaired *t* test. Data are reported as mean ± SD.

A comparison between study centers was also performed to insure that patient groups were similar in each institution. A standardized scoring system, the Score for Neonatal Acute Physiology (SNAP), was computed for each neonate.[23] The resulting score was similar between study sites.

The primary outcome (CB) was then assessed using a multivariate regression analysis. To evaluate all covariates, the regression equation was performed using backward elimination, and strong collinearity was found between gestational age and birth weight. Therefore, birth weight was excluded from the final model. In the final model, CB was regressed against taurine, controlling for the effects of gestational age, diagnostic group, and CCK. Even though CCK did not have an effect on PNAC, it was included as a covariate in this analysis to eliminate the possibility of any effect on CB. Analysis was done with SAS 8.2 software (SAS Institute, Inc, Cary, NC).

Secondary outcomes of the 2 groups (with or without taurine) were compared using a *t* test for continuous covariates or Fisher's exact test for categorical covariates. Days to 50% and 100% enteral intake were treated as continuous variables. Sepsis and mortality were treated as dichotomous categorical variables.

RESULTS

A total of 243 patients were enrolled in the study. Of these, the status of PN (with/without taurine) was unknown in 7, and therefore only 236 were included in the analysis. The baseline characteristics of the study population are shown in Table I. Although the mean gestational age differed (by *t* test) between the 2 groups (Table I), this was attributable to a clear skew in the distribution of ages. Thus, the median gestational age was identical in both groups (26 weeks). Furthermore, the distribution of patients was similar in both groups, with the majority of subjects being ≤30 weeks (with taurine, 75.4%; without taurine, 92.7%). Thus, the direction of skew was the same in both groups but was stronger in the group without taurine, leading to a different mean gestational age. The distribution of birth weight followed the same pattern as that of gestational age, although the skew was not quite as pronounced (Table I). Finally, there were more older, surgical neonates in the with taurine group. Nevertheless, to control for the possible effect of gestational age and birth weight as confounders, both these covariates were entered into the initial regression model. The primary regression equation demonstrated strong collinearity between these 2 variables. In other words, gestational age correlated very strongly with birth weight, and thus only 1 of these 2 variables could be treated as an independent covariate. Therefore, only gestational age was included in the final model.

The final model was highly significant ($p < .0001$) and therefore predictive of CB. It was necessary to combine patients with a diagnosis of gastroschisis with those having intestinal atresia due to the low number in these 2 groups ("Surgical" group). Thus, stratification groups are reported as Premature, NEC, or Surgical. NEC was a significant predictor of PNAC (β estimate = 3.01, $p < .0001$). The β estimate indicates how much a given covariate influences the predicted CB. Thus, this means that the CB of an infant with NEC is predicted to be 3.01 mg/dL greater than that of

TABLE I
Characteristics of the study subjects

PN formula with taurine, without taurine	With taurine, $n = 195$	Without taurine, $n = 41$	p*
Gestational age at enrollment (weeks) median:	28.1 ± 4.4 (26.0)	26.5 ± 2.7 (26.0)	.04
Total: $n = 236$	$n = 195$	$n = 41$	
Birthweight (g; median)	1172.6 ± 813.3 (831)	914.0 ± 468.4 (815)	.05
Total: $n = 236$	$n = 195$	$n = 41$	
Septic episode			
Yes	98 (50.3%)	25 (61.0%)	.23
No	97 (49.7%)	16 (39.0%)	
Death			
Yes	29 (14.9%)	7 (17.1%)	.81
No	166 (85.1%)	34 (82.9%)	
Days in neonatal intensive care unit (median)	67.8 ± 37.3 (71)	74.7 ± 42.5 (84)	.31
Total: $n = 228$ (missing data: $n = 8$)	$n = 189$	$n = 39$	
Days in hospital (median)	74.3 ± 41.8 (76.5)	76.4 ± 41.6 (86)	.77
Total: $n = 224$ (missing data: $n = 12$)	$n = 186$	$n = 38$	
Time to achieve 50% caloric intake *via* the enteral route (days)	24.9 ± 17.2	27.9 ± 18.1	.39
Total: $n = 172$ (missing data: $n = 64$)	$n = 143$	$n = 29$	
Time to achieve 100% caloric intake *via* the enteral route (days)	30.1 ± 17.8	27.0 ± 13.7	.40
Total: $n = 174$ (missing data: $n = 62$)	$n = 147$	$n = 27$	

Data shown are mean ± SD. Numbers in parentheses are percentages for sepsis and death and median for all other variables.
*Comparisons made with 2-tailed unpaired t test for continuous variables, and with Fisher's exact test for dichotomous variables.

an infant not having NEC, all other factors being equal. The analysis considered all possible interactions. Although analyzing the potential effect of each covariate on CB, all other covariates were held constant. Other β estimates are shown in Table II. Premature and Surgical groups did not significantly predict the risk of PNAC (Table II).

When all stratification groups were analyzed together (Premature, NEC, and Surgical), taurine did not have a significant effect on CB (Table II). In other words, for all data in aggregate, the presence of taurine did not achieve significance as a predictor of CB. However, when the effect of taurine was considered within each stratification group, taurine supplementation was beneficial for premature and NEC infants (Figure 1). The potential effect of taurine supplementation in the Surgical group could not be determined, due to the low number of patients in this latter group. The predicted

TABLE II
Final multiple regression model predicting conjugated bilirubin

Overall model	β Estimate (95% confidence interval)	p
F statistic	6.71	<.0001
Intercept	3.15 (2.00 to 4.30)	<.0001
Treatment effect (CCK or placebo)	−0.08 (−0.48 to 0.32)	.70
Diagnostic group effect		
Premature	−1.17 (−2.73 to 0.32)	.12
NEC	3.01 (1.55 to 4.48)	<.0001
Surgical	−1.84 (−4.32 to 0.64)	.15
Taurine effect	−0.04 (−1.20 to 1.11)	.94
Age effect	0.36 (−0.001 to 0.73)	.06
Interaction effect of taurine in specific groups		
Premature and taurine	−1.40 (−2.92 to 0.12)	.07
NEC and taurine	−2.15 (−3.68 to −0.61)	.006

The β estimate can be understood as an estimate of the risk of the predicted outcome. Thus, the conjugated bilirubin (CB) of an infant with necrotizing enterocolitis (NEC) is predicted to be 3.01 mg/dL greater than that of an infant not having NEC, all other factors being equal. The analysis considered all possible interactions. In considering the potential effect of each covariate on the outcome (CB), all other covariates were held constant. Although taurine did not significantly predict overall CB, it was a significant covariate when examined within the Premature and NEC groups (but not within the Surgical group, due to low numbers of patients in that group). The treatment effect of cholecystokinin-octapeptide (CCK) was not significant (as reported separately). CB, conjugated bilirubin; NEC, necrotizing enterocolitis.

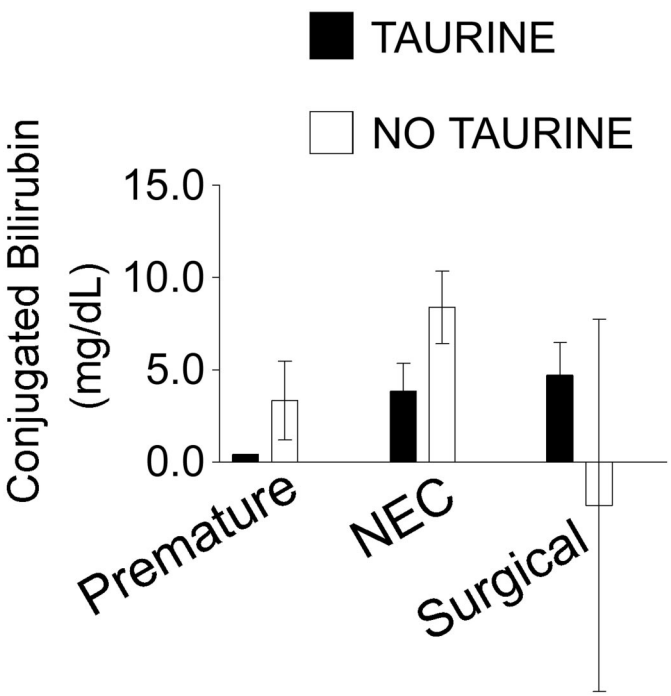

FIGURE 1. Estimated maximum conjugated bilirubin levels (error bars denote the 95% confidence intervals) are shown for neonates stratified into the Premature, NEC (necrotizing enterocolitis) or Surgical groups. By multiple regression analysis, taurine reduced the risk of PNAC in premature infants and infants with NEC. Variation was too great in the Surgery group (gastroschisis and intestinal atresia) to achieve significance. Negative values of bilirubin in the Surgery group indicate the inability of the regression model to significantly predict CB in that group.

maximum CB for each stratification group is shown in Figure 1.

Predicted CB was reduced in premature infants receiving taurine (predicted CB [95% confidence interval] 0.50 mg/dL [−0.17 to 1.18]), *vs* premature infants not receiving taurine (3.45 mg/dL [1.79–5.11], $p = .07$). Taurine also significantly reduced the predicted CB in infants with NEC (4.04 mg/dL [2.85–5.23], NEC infants receiving taurine; *vs* 8.29 mg/dL [5.61–10.96], NEC infants not receiving taurine, $p < .01$).

Secondary outcomes examined by Fisher's exact test revealed a somewhat lower mortality rate (14.9% *vs* 17.1%) and a lower rate of sepsis (50.3% *vs* 61.0%) in the group receiving taurine, but neither of these reductions was significant (Table I). Similarly, the number of days in the neonatal intensive care unit (68 ± 37 days) and hospital days (74 ± 42) were lower on average in the taurine-supplemented group *vs* the group without taurine (75 ± 43, and 76 ± 42 days, respectively), but again, these differences were not significant (Table I). The length of time to wean off PN (as measured by achieving 50% and 100% enteral intake) did not differ significantly between the taurine and nontaurine groups; but it was evident that the average patient was dependent on receiving PN for approximately 1 month, an adequate time period for the development of PNAC. There were not enough patients to perform a meaningful subset analysis of each of these secondary outcomes (mortality, sepsis, hospital/intensive care stay, and duration of PN) within each stratification with or without taurine.

DISCUSSION

The possibility that taurine may prevent PNAC in human neonates has been debated for more than 20 years, but no large clinical study has previously answered this question. Much has been learned about the risk factors and morbidity of PNAC,[2–9,24] but a causative link between taurine deficiency and neonatal PNAC has not been demonstrated conclusively. The assertion that taurine supplementation prevents PNAC has been based on animal studies,[10–11] observations of taurine deficiency in children receiving PN,[9,12] and the fact that taurine deficiency can be corrected in these children by providing parenteral taurine.[13,14] The present study substantially strengthens the evidence for a preventive role of taurine in human neonatal PNAC.

PNAC is a diagnosis of exclusion. As such, an important component of the current study was exclusion of all known potential causes of cholestasis other than PN. Incomplete exclusion of non-PN causes of cholestasis has compromised a number of studies of PNAC. Our study, however, also has clear limitations. It was not randomized or blinded. Unknown potential confounders may have influenced which patients received taurine and which did not. However, we did seek to minimize all known confounding variables by striving for homogeneity between study sites in all parameters other than taurine.

In addition, the multivariate analysis was designed to take into account the potentially confounding effects of multiple covariates. One potential confounding factor is the gestational age of infants in the 2 groups (with or without taurine). Although the median gestational age in each group was 26 weeks, the mean gestational age differed between the groups, most likely due to the predominance of older surgical patients in the taurine group. Therefore, we entered gestational age into the model as a covariate and held this covariate constant while analyzing the effect of other covariates on CB. Because we controlled for gestational age in the multivariate regression, our findings should be independent of a possible effect of gestational age on CB. Clearly, prospective enrollment of randomized or age-matched patients might offer a stronger analysis.

Another potential limitation of the study was the fact that choice of PN formulation was not controlled by the investigators. Addition of taurine to the pediatric amino acid formulas is a salient distinction from adult formulas, but the presence of cysteine is an additional factor that may contribute to protection against PNAC. However, this additional protection may very well be directly due to taurine because cysteine is a direct precursor of endogenous taurine synthesis.[25,26] Cysteine supplementation may provide protection against PNAC by simply enhancing the rate of endogenous taurine production.[25–28] Studies have documented normalization of serum taurine levels in children receiving cysteine-supplemented PN.[28]

It would probably not be ethical to perform a randomized study of the effect of taurine supplementation in premature and critically ill neonates. In particular, evidence has been available for quite some time that increasingly suggests a requirement for taurine in the development of the retina.[29,30] According to this fact, hospital formularies have progressively moved from standardized adult crystalline amino acids to specially designed pediatric formulas containing taurine. However, the transition between these parenteral solutions has provided for a unique opportunity to gather data in a large subset of newborn patients that may not be repeatable in the future. Importantly, the choice of taurine supplementation in neonatal PN was based on individual hospital formulary decision and not by the investigators. By the end of the study period, all institutions involved had acquired taurine-containing PN formulations for neonatal use.

The magnitude of protection afforded by taurine was strongly affected by the patient's diagnosis. This point is emphasized by the fact that when the entire group of patients is examined together, no preventive effect on PNAC is seen. This is most likely explained by the fact that infants in the surgical group showed no significant influence (either positive or negative) on CB due to taurine. These infants tended to be somewhat older than the premature group but also tended to have more significant comorbidities, complicated hospitalizations, and more potentially confounding variables. The premature infants and the infants with NEC benefited from taurine supplementation. The magnitude of the benefit was a decrease in estimated CB of about 2.95 mg/dL for premature infants receiving taurine and a decrease of about 4.25 mg/dL for NEC infants receiving taurine (Figure 1). This reflects the fact that NEC infants tended to have higher CB overall.

The causes of PNAC are almost certainly multifactorial, and amino acid use changes with development of the fetal liver. It is possible that other factors, such as immaturity of bile canalicular transport proteins, may have a greater role in the development of PNAC in very premature infants as opposed to older infants,[31] and bile canalicular transport dysfunction would likely predispose to PNAC independent of whether taurine is administered. Extreme prematurity may present new challenges to the ongoing improvement of PN. The ability of the premature kidney to conserve taurine is significantly compromised, which may exacerbate taurine deficiency in these patients.[32] As serum taurine levels were not determined in this study, it is difficult to know whether the levels were completely normalized in each stratification group, although previous studies would suggest that this was the case.[14]

Taurine is synthesized *via* the transulfuration pathway, in which the eventual conversion of methionine to homocysteine to cystathionine requires conversion of cystathionine to cysteine *via* cystathionase, which is further converted to taurine. However, neonates are deficient in cystathionase and are thus especially susceptible to a loss of exogenous sources of taurine.[25,26] Significantly, human breast milk is rich in taurine,[33] and even formula-fed infants are found to have lower taurine levels than breast-fed infants.[27] Because cysteine is a precursor of taurine, provision of cysteine can correct the deficiency of taurine associated with long-term PN.[28] The cellular mechanisms by which taurine achieves its clinical effects probably include increased secretion of bile and improved bile acid conjugation.[10,11] Bile acid conjugation in the human fetal liver demonstrates a preference for taurocholate synthesis over glycocholate, in contrast to the mature liver.[34,35] More recent work has found that taurine may enhance the phagocytic activity of neutrophils, thus promoting innate immune defenses.[33] Whether this might prevent hepatic dysfunction is unknown. Further work will be needed from the basic science perspective to elucidate the subcellular actions of taurine.

In summary, we have conducted a multivariate analysis of a large group of neonatal patients receiving PN with or without taurine. Taurine-supplemented PN exerted a significant protective effect against PNAC in infants with prematurity or NEC. This finding confirms previous studies suggesting a link between PNAC and taurine deficiency. We believe this study provides a strong argument for the use of taurine in all neonatal crystalline amino acid PN formulas.

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Discussant

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Comments

I commend this group for the great work that has been done. This study provides strong evidence for the use of taurine in preventing PNAC in human neonates and further confirms previous studies linking PNAC and taurine deficiency. Neonates receiving parenteral nutrition are at risk for PN-associated cholestasis. Mutivariate analysis of 236 neonates receiving PN with or without taurine revealed a reduction in conjugated bilirubin in neonates with prematurity or necrotizing enterocolitis receiving taurine.

Questions

1. Could you elaborate on the dosages of taurine per day used in this study and recommendations for practitioners?
2. How often did you monitor taurine levels and what were your findings? Do you have recommendations for clinicians?
3. Would you like to comment on the next step with this research? Implications for further research?

Author's Response

Thank you for these insightful questions. In reply to the first question, the dose of taurine per day was dependent on the total amount of protein administration (which was titrated by the clinicians caring for each infant) and also on the amino acid formulation used (which was either Trophamine or Aminosyn-PF). The dose (of taurine only) ranged from 6.0 to 21.6 mg/kg/d. However, considering the sum of taurine *plus* its direct precursor, cysteine, these 2 formulas are actually very similar, and the effective delivery of taurine was probably closer to 14.0–18.0 mg/kg/d. Cysteine is converted directly to taurine. We suspect that much of the literature regarding the potential benefits of cysteine may actually be evidence for an effect of improved endogenous taurine synthesis, as we have discussed in the full paper.

In reply to the second question, we did not monitor taurine levels. This has already been done by previous investigators; and importantly, it has been shown that the same taurine-containing formulations used by patients in our study do, in fact, normalize the serum levels of taurine in infants and children. We have cited these previous studies in our paper. Unless there is a specific cause for concern regarding the adequacy of taurine provision, the clinician probably does not need to routinely assess serum taurine levels in the neonate receiving taurine-supplemented PN.

The third question truly addresses a concern relevant to all of us: whether we may be able to more clearly elucidate the underlying causes of neonatal parenteral nutrition–associated cholestasis. Bile acid transport systems, which may not be fully developed in

the premature neonate, may play a significant role in the development of cholestasis. The clinical factors predisposing to cholestasis, such as sepsis, prematurity, and intestinal stasis, lead us to believe that the etiology of PNAC is probably complex and multifactorial. We have a current strong interest in animal models of PN administration and are looking at new directions for the molecular pathophysiology of PNAC.