CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-678/S003

ADMINISTRATIVE DOCUMENTS

ORIGINAL

20-734

MEMORANDUM OF A T/CON
DIVISION OF METABOLISM AND
ENDOCRINE DRUG PRODUCTS (HFD-510)

MEETING DATE: July 28, 1999 **TIME:** 9:00am

SPONSOR: Baxter

DRUG: Large Volume Injection Amino Acids

NDAs: 19-520/S-018; 20-047/S-006; 20-734/S-003; 20-678/S-003

TYPE OF MEETING: Advice Meeting

MEETING CHAIR: Eric Colman, Medical Reviewer

MEETING RECORDER: Steve McCort, Project Manager

PARTICIPANTS:

FROM FDA:

Eric Colman, Medical Reviewer (HFD-510)
Steve McCort, Project Manager (HFD-510)

FROM BAXTER:

Linda Colman, Regulatory Affairs
Dean Snyder, Regulatory Affairs

MEETING OBJECTIVE:

To discuss the revisions in the labeling for approved LVP products containing amino acids in response to the Federal Register Notice requiring updated information on pediatric use of the products.

BACKGROUND:

Baxter Healthcare submitted labeling supplements to parenteral LVPs containing Amino Acids in response to the Final Rule published in the Federal Register Notice titled "Specific Requirements on Content and Format for Human Prescription Drugs: Revision of "Pediatric Use" Subsection in the Labeling." On review of these supplements Dr. Eric Colman reviewer requested a telephone conference with Baxter to inquire why they had revised the labeling before a meeting with ——was to be held to address the pediatric labeling issue with other firms present. In addition Dr. Colman had several other concerns with the labeling he wished to discuss.

DISCUSSION:

The purpose on the call was to ask the Sponsor:

1. Why the labeling revisions were made for these Amino Acid products since the firm was thought to be participating in a — sponsored program in which the firms that have similar LVP products could meet to agree to a common revision and submit their proposal to FDA for comment.

2. To address specific comments from the medical reviewer regarding the firm's recent labeling supplements.

Regarding point #1 Baxter decided to submit the pediatric labeling supplements since the interactions with — have not been productive. —

— Dr. Colman suggested that Baxter continue to work with —regarding this issue.

Regarding Point 2, Dr. Eric Colman, had concerns regarding the proposed labeling revisions for the above supplements. The firm had proposed additions to the Warning section a statement regarding (1) addition of a new Warning relating to the administration of dextrose to low birth weight infants; (2) incorporation of a new Pediatric Use" subsection in the Precautions section regarding the use in the pediatric population, a revision to the last sentence in the Dosage and Administration and Administration section. No decision was made at this time regarding Baxter's proposed labeling revisions. The issue will be deferred until the issue is discussed with other competing manufacturers.

CONCLUSIONS:

1. Baxter has deferred working with — regarding a common proposal for pediatric labeling revisions for LVP products containing amino acids. However Baxter was told to continue working with — on this issue.

2. Comments regarding the labeling supplements by the Agency will be deferred until the other issue of pediatric labeling revisions for nutritional LVPs containing amino acids are discussed with the other competing manufacturers.

Signature of Minutes preparer: /S/ 8-10-95
Steve McCort
Project Manager, HFD-510

Signature of Meeting Chair: /S/ 8/11/95
Eric Colman, M.D.
Medical Reviewer, HFD-510

cc: NDA 19-520/S-018; 20-047/S-006; 20-734/S-003; 20-678/S-003
HFD-510/DivFiles
HFD-510/EColman/SMcCort

Author: Linda Coleman at wg1003
Date: 2/17/00 4:50 PM
Priority: Normal
): "Stephen McCort 301-827-6415 FAX 301-443-9282" <MCCORTS@cder.fda.gov> at BAXTER
ubject: Re: FWD: Pediatric Labeling for Amino Acid Solutions
---------- Message Contents ----------

Steve,

In follow-up to our conversation today, Baxter agrees with the Agency's proposed wording for pediatric use of amino acid products with the exception of the last sentence in the Pediatric Use subsection of DOSAGE AND ADMINISTRATION. The Agency proposed the following sentence:

[ ]

Instead, Baxter recommends the following statement:

"Solutions administered by peripheral vein should not exceed twice normal serum osmolarity (718 mOsmol/L)."

Baxter believes the sentence proposed by the Agency ~~~~~ ~~~~~ Solution osmolarity is not as much of concern when parenteral nutrition is administered via central vein because of dilution at this site. Therefore, the statement regarding solution osmolarity should specifically apply to peripheral vein administration only.

Linda Coleman

---------- Reply Separator ----------
Subject: FWD: Pediatric Labeling for Amino Acid Solutions
Author: "Stephen McCort 301-827-6415 FAX 301-443-9282" <MCCORTS@cder.fda.gov> at BAXTER
Date: 2/11/00 3:11 PM

letter we spoke about

Content-Transfer-Encoding: 7bit
Date: Fri, 11 Feb 2000 15:58:27 -0500 (EST)
Date: Fri, 11 Feb 2000 15:58:30 -0500 (EST)
From: "Stephen McCort 301-827-6415 FAX 301-443-9282" <MCCORTS@cder.fda.gov>
Subject: Pediatric Labeling for Amino Acid Solutions
To: colma@baxter.com
cc: "Moshe Zilberstein" <ZILBERSTEINM@cder.fda.gov>, "Eric Colman" <COLMANE@cder.fda.gov>, "Stephen McCort" <MCCORTS@cder.fda.gov>
Message-ID: <C2266IIB3FPX7*/R=A1/R=FDACD/U=MCCORTS/@MHS>
Delivery-date: Fri, 11 Feb 2000 15:58:00 -0500 (EST)
Posting-date: Fri, 11 Feb 2000 15:58:30 -0500 (EST)
Importance: normal
Priority: normal
Sensitivity: Company-Confidential
-type: MAIL
ntent-Type: multipart/mixed; boundary="Boundary_(ID_5txEphbP9y63qp+ZJVujbg)"

FOOD AND DRUG ADMINISTRATION

DATE: **MARCH 14, 2000**

DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS, HFD-510
DOCUMENT CONTROL ROOM 14B-19
5600 FISHERS LANE
ROCKVILLE, MARYLAND 20857

TO:		FROM:	
Name:	**LINDA COLMAN**	Name:	**Steve McCort**
Fax No:	847-270-4668	Fax No:	301-443-9282
Phone No:	847-270-2577	Phone No:	301-827-6415
Location:	BAXTER	Location:	FDA, Division of Metabolic and Endocrine Drug Products

Comment:

REQUEST FOR PEDIATRIC SUPPS

APPEARS THIS WAY
ON ORIGINAL

For the following NDA Supplements:

NDA 19-520/S-018, 20-147/S-006, 20-678/S-003, 20-734/S-003

Please send to me the following:

1. EA - Request for Categorical Exclusion
2. Patent Certification
3. Debarment Certification
4. Financial Disclosure Statement may be needed. I will let you know

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 5, 2000

FROM: Steve McCort

SUBJECT: Summary of Information to Support the Pediatric Information in the Labeling

TO: File for NDAs 19-520/S-018, 20-147/S-006, 20-678/S-003, 20-734/S-003

The Sponsor did not submit an Integrated Summary of Effectiveness or Integrated Summary of Safety Sections to support the labeling revisions to the WARNINGS, PRECAUTIONS, and DOSE AND ADMINISTRATION sections in the labeling for the above products. However the Sponsor submitted literature that included clinical studies to support the their labeling revisions. This section includes the following:

1. A copy of the original cover letter which includes the relevant information in the submission.

2. Attachment 3 - Bibliography of General Articles

3. Attachment 6 - Bibliography of Medical Textbook References

4. Attachment 7 - Dextrose Pediatric Labeling Support Information

/S/

Steve McCort
Project Manager, HFD-510

APPEARS THIS WAY
ON ORIGINAL

I.V. Systems Division
Regulatory Affairs

Baxter Healthcare Corporation
Route 120 & Wilson Road
Round Lake, Illinois 60073-0490

847.270.4637
Fax: 847.270.4668

Baxter

ORIGINAL

July 6, 1999

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
Division of Metabolism and Endocrine Drug Products, HFD-510
Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857-1706

NDA NO. 20-678 REF NO. 003
NDA SUPPL FOR SE1
SE1-003

Re: NDA 20-678: Clinimix E™ sulfite-free (Amino Acid with Electrolytes in Dextrose with Calcium) Injections in Clarity™ Dual Chamber Container Supplemental Application - Pediatric Labeling Statements

Dear Colleague:

Baxter Healthcare Corporation is submitting this supplemental application in response to the Final Rule published in the Code of the Federal Register on December 13, 1994, titled *Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of "Pediatric Use" Subsection in the Labeling,* vol. 59, No. 238, pages 64240-64250.

The content and format of this supplemental application are consistent with the Guidance for Industry document titled *The Content and Format for Pediatric Use Supplements* dated March, 1996. A completed 356h application form and a User Fee form are attached to this cover letter. The information in support of this supplemental application is provided following this cover letter.

If you have any questions, please contact me or Linda Coleman at (847) 270-2577.

Sincerely,

Marcia Marconi
DSL

Marcia Marconi
Vice President, Regulatory Affairs
phone: (847) 270-4637
fax: (847) 270-4668

REVIEWS COMPLETED	
CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO	
CSO INITIALS	DATE

JUL 6 1999

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NDA 20-678: Clinimix E™ sulfite-free (Amino Acid with Electrolytes in Dextrose with Calcium) Injection in Clarity™ Dual Chamber Container
Pediatric Labeling Supplement

I. Content and Format

A. Labeling

1. Draft Revised Labeling

Draft revised labeling is provided in **Attachment 1**. This labeling reflects (1) addition of a new Warning statement relating to administration of dextrose to low birth weight infants; (2) incorporation of a new "Pediatric Use" subsection in **Precautions** regarding considerations for use in the pediatric population; (3) a revision to the last sentence in the third paragraph of **Dosage and Administration**; and (4) a new "Pediatric Use" statement in **Dosage and Administration**; and (5) an additional statement in "Peripheral Vein Administration" in **Dosage and Administration**.

The new "Warning" reads as follows:

"In very low birth weight infants, excessive or rapid administration of dextrose injection may result in increased serum osmolality and possible intracerebral hemorrhage."

The new "Pediatric Use" statement under **Precautions** reads as follows:

*"**Pediatric Use:** Dextrose is safe and effective for the stated indications in pediatric patients (see **Indications and Usage**). As reported in the literature, the dosage selection and constant infusion rate of intravenous dextrose must be selected with caution in pediatric patients, particularly neonates and low birth weight infants, because of the increased risk of hyperglycemia/hypoglycemia. Frequent monitoring of serum glucose concentrations is required when dextrose is prescribed to pediatric patients, particularly neonates and low birth weight infants.*

*However, the use of amino acid injections in pediatric patients as an adjunct in the offsetting of nitrogen loss or in the treatment of negative nitrogen balance is well established in the medical literature. See **Dosage and Administration.**"*

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The last sentence in the third paragraph of **Dosage and Administration** reads as follows:

"Daily amino acid doses of approximately 1.0 to 1.5 g/kg of body weight for adults with adequate calories are generally sufficient to satisfy protein needs and promote positive nitrogen balance."

The following "Pediatric Use" statement has been added to **Dosage and Administration:**

***"Pediatric Use:** Use of Clinimix™ - sulfite-free Injections in pediatric patients is governed by the same considerations that affect the use of any amino acid solution in pediatrics. The amount administered is dosed on the basis of grams of amino acids/kg of body weight/day. Two to three g/kg of body weight for infants with adequate calories are generally sufficient to satisfy protein needs and promote positive nitrogen balance. Solutions administered by peripheral vein should not exceed twice normal serum osmolarity (718 mOsmol/L)."*

The following statement has been added to "Peripheral Vein Administration" in **Dosage and Administration:**

"In pediatric patients, the final solution should not exceed twice normal serum osmolarity (718 mOsmol/L)."

2. Marked-up, Annotated Copy of Current Labeling

Attachment 2 contains a marked-up copy of the current labeling, clearly showing all additions and deletions, with annotations as to where the supporting data are located in the submission.

B. Regulatory Basis for Labeling Change

Amino Acids

We are revising the amino acid labeling for these products in accordance with 21 CFR 201.57(f)(9)(vi). Our search of the medical literature has not found adequate and well-controlled studies in pediatric patients using amino acid injections as indicated by the current labeling. However, the use of amino acid injections in pediatric patients as an adjunct in the offsetting of nitrogen loss or in the treatment of negative nitrogen balance is well established in the medical literature. See **Dosage and Administration.**

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21 CFR 201.57(f)(9)(ii) does not apply since our search of the medical literature does not provide any information supporting an indication for the pediatric population different from that approved for the adult population.

21 CFR 201.57(f)(9)(iii) does not apply since our search of the medical literature does not provide adequate and well-controlled studies to support a pediatric indication similar to the current adult indication.

21 CFR 201.57(9)(v) does not apply because the literature does not contain adequate and well-controlled studies in any particular pediatric population to support a pediatric labeling claim.

21 CFR 201.57(f)(9)(vii) does not apply since we have selected sub-paragraph (vi) as the basis for our proposed labeling change.

21 CFR 201.57(f)(9)(viii) does not apply since the product does not contain one or more inactive ingredients that present an increased risk of toxic effect.

Dextrose

Pediatric use labeling supplements relating to dextrose were submitted to ANDAs 16-673/S-122, 16-694/S-098, and 20-179/S-003 on June 7, 1996. Those supplements, with some modifications to the proposed labeling, were found approvable in a letter to Baxter dated March 30, 1999. We are enclosing as **Attachment 7** a copy of the Content and Format section of that supplement and a copy of FDA's letter dated March 30, 1999, containing required modifications to the labeling proposed in that supplement. The changes proposed in this supplement relating to dextrose are identical to the changes, as modified, found approvable in the letter dated March 30, 1999..

C. 21 CFR 201.57(f)(9)(iv) as Regulatory Basis for Labeling Change

Not Applicable.

D. The Age Categories for which Pediatric Data are Being Submitted.

The literature articles submitted with this correspondence pertain to the age categories neonates, infants, children, and adolescents.

E. Identification of Data Submitted for Each Age Category.

See **Table 1** on the following page for the identification of data submitted.

Table 1

Age Range and Data Type Category for Pediatric Use Data

Type of Data	Neonates (Birth up to 1 month)	Infants (1 month up to 2 years)	Children (2 years up to 12 years)	Adolescents (12 years up to 16 years)
Pharmacokinetic/ Pharmacodynamic				
- Raw Data				
- Literature				
Clinical Efficacy				
- Raw Data				
- Literature				
Safety/Adverse Reaction From Clinical Studies				
- Raw Data				
- Literature	X	X	X	X
From Anecdotal Reports				
- Medwatch/3500s				
- Literature				
- Literature Reference/ Raw Data				

F. Summary of information submitted to support the pediatric labeling statements

Development of the proposed labeling statements was the result of evaluating existing clinical literature reporting on the use of amino acid injections in pediatric patients.

Literature searches resulted in a total of 33 relevant articles. A bibliography of these articles is provided in **Attachment 3**. The method of search is described in **Section II. Presentation of Data.** All the articles were evaluated for content, and twenty-three articles were placed into an information database created by an outside consulting firm, [redacted] A copy of the information database created by [redacted] is provided in **Attachment 5**. Ten studies were not evaluated because (1) they did not examine amino acid products; (2) they did not examine the efficacy of amino acid solutions in pediatric patients; (3) they examined only adult patients; (4) they were review articles; or (5) they were unpublished abstracts.

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Besides the 33 articles identified in the literature search, two additional relevant articles were evaluated. A bibliography and copies of those articles are found in **Attachment 6.**

The resulting database was reviewed for:

1. Interactions and Warnings Concerning Administration of Amino Acids
2. Serious Adverse Reactions
3. Nonserious Adverse Reactions
4. Labeled Dosage and Administration Instructions Relative to Studies with Serious and Nonserious Adverse Reactions

All articles with such information were thoroughly reviewed for information that might affect the product labeling for use in pediatric patients. The following is a summary of articles that meet the criteria described above. The study number referenced is a Baxter-assigned identification number specific to the article and can be cross-referenced to the bibliography in **Attachment 3**. Actual copies of literature articles reviewed below are in **Attachment 4**.

1. Interactions and Warnings Concerning Administration of Amino Acids

None.

2. Serious Adverse Reactions

Anaphylactic Episode

Study #22--Reports one case of an anaphylactic reaction in a 4-year-old boy hospitalized for closure of a colostomy performed perinatally due to a high imperforate anus. Within 15 minutes of initiation of parenteral nutrition, the child developed a tachycardia of 180 beats/min with unmeasureable blood pressure, a severe stridor, a dyspnea with 35 strenuous breaths/min, cyanosis and generalized edema of the skin. The parenteral nutrition was stopped and within several minutes the stridor and dyspnea improved and the cyanosis evolved to pallor. Ten weeks after the anaphylactic episode, dermal allergy tests were performed. They demonstrated a sensitivity to the Travasol® solution, to $MgSO_4$, and to multivitamin 12.

Death

Study #32--Reports one case of death occurring in an infant who received Aminosyn (Abbott Laboratories) solution without incident for two weeks but who died of respiratory failure due to severe bronchopulmonary dysplasia at five weeks of age.

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Hyperammonemia
Study #33--Four infants developed lethargy or frank coma in association with blood ammonia concentrations ranging from 250 to 620 µg/dL. Symptoms resolved and blood ammonia fell when TPN was discontinued or the protein content was decreased. Five other patients who had blood concentrations in the same range remained asymptomatic. No patient developed symptoms while blood ammonia was less than 250 µg/dL.

3. Nonserious Adverse Reactions

Complications from liver disease
Study #6--Compared a BCAA (branched chain amino acids) enriched formulation with a standard enteral formulation in children with end stage liver disease. The incidence of complications of liver disease was similar on both treatment arms. Nine episodes of cholangitis or sepsis occurred on the standard enteral formulation whereas eight episodes occurred on the BCAA formulations; six episodes of gastrointestinal bleeding occurred on both arms and one encephalopathic episode occurred on each, with no appreciable rise in serum ammonia concentrations.

Elevated BUN
Study #23--Ten very low birth weight infants requiring TPN were studied to evaluate their metabolic response to the amino acid solution Travasol® 10% blend C. One patient had an elevated BUN (41 mg/dL). All others were within the normal range for very low birth weight infants (15 ± 4 mg/dL). The authors concluded that Travasol® blend C produced no short-term imbalance of the plasma aminogram of very immature low birth weight infants.

4. Labeled Dosage and Administration Instructions Relative to Studies with Serious and Nonserious Adverse Reactions

Study #6--85 - 100 mL/kg per day of enteral formulation depending on the age of the patient.

Study #22--Anaphylactic reaction after 15 minutes of administration of 2.75% Travasol® Injection and 10% dextrose.

Study #23--Constant peripheral intravenous infusion of amino acids (2.61±0.02 g/kg/day), fat emulsion (2.0±0.1 g/kg/day), and dextrose (12.8±0.1 g/kg/day) for 4.6±0.3 days before blood sampling.

Study #32--Neopham (Cutter Laboratories): 2.56±0.4 g/kg/day; Aminosyn (Abbott Laboratories): 2.69±0.4 g/kg/day.

Study #33--Amigen (Baxter Healthcare Corporation) and FreAmine II (McGaw Laboratories): Early in this series, a few patients received up to 4.5 g/kg/day of protein. Since 1974, all infants have received a standard 2% protein solution providing 2.5 to 3.0 g/kg/day of protein. Older children received 1.5 to 2.0 g/kg/day of protein. Travasol: 2.5 to 3.0 g/kg/day of protein.

II. Presentation of Data

A. The source of the data

Data supporting the proposed labeling revisions were derived from literature articles and other references pertaining to the use of amino acid injections in the pediatric population. Bibliographies of the articles are provided in **Attachments** 3 and 6. Actual copies of the literature articles referenced are in **Attachments** 4 and 6.

The search strategy for articles regarding the use of amino acid injections in pediatric patients included a literature search by Baxter's Information Management Center to locate published studies, case reports, and other documentation pertaining to the use of amino acids in the pediatric population. Two databases were used: Medline was searched from 1966 to July 1995 and International Pharmaceutical Abstracts was searched from 1970 - July 1995. The starting dates for these searches were the earliest dates the databases are available in an electronic, searchable form. The vendor of these databases is ——— and its search conventions were used. The search strategies for each database are described below.

Medline
The free text term "travasol??" or variations thereof was searched. This was then cross-referenced with the exploded term "child", which includes terms identifying infants, children or adolescents. In addition the term "amino acids, branched-chain" (bcaa) was exploded using the subheading for administration and dosage. This statement was then cross-referenced with the exploded terms "infusions, parenteral", "injections, intravenous", or "infusion pumps". Bcaa was also cross referenced with infus?, parenteral? or inject?, or intravenous? in the title. These two sets were then combined ("or") into one large statement and cross-referenced with the exploded term "child", which includes terms identifying infants, children, or adolescents.

International Pharmaceutical Abstracts

The free text term "travasol" and variations thereof were searched. This was then cross-referenced with the free text terms "child", "pediatric", "newborn", "infant", "neonate" or "adolescent" or variations thereof. In addition both the descriptor fields and free text were searched for the terms isoleucine?, leucine?, or valine?, which are the principal branched chain amino acids. The character string "branched(w)chain(w)amino(w)acid?"[(w) is the ~~~ convention for adjacency] was also searched. This was then combined with the truncated free text terms infus?, inject?, parenteral?, intravenous? or syringe?. Admin? or iv in the title in combination with the terms for bcaa was also searched. The bcaa terms were also combined with the truncated subject headings infusion?, syringe?, or inject?. These three sets were combined into one large statement and cross referenced with the truncated terms child?, pediat?, newborn?, infant?, neonat?, or adoles?.

Besides the 33 literature articles, two additional references were identified as sources to support certain proposed labeling changes. Those two references are listed in **Attachment 6** and copies are included in **Attachment 6**.

B. A summary of the articles selected in support of the proposed labeling statements is in **Table 2**.

C. Analysis of Data

See **Section I.F.**

D. Extent of exposure, duration of exposure, and adverse events.

See **Table 2** for extent and duration of exposure. See **Section I.F.** for adverse events.

E. Description of formulation, route of administration, and acceptability for pediatric use.

See **Table 2** for formulation and route of administration.

F. The drug product does not contain any excipients that present an increased risk of toxic effects in the pediatric population.

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Table 2

Types of Studies and Design Features

ID	Investigator	Publication	Purpose of Study	Age of Subjects	Number of Patients	Formulation/ IV Dosage	Dosage and Administration	Duration
1	Blazer S, Reinersman GT, et al.	J Perinatol 14(4):290-5, 1994	"The aim of this study was to compare the effects of infusing a BCAA (branched-chain amino acids)-enriched TPN (total parenteral nutrition) solution (53% BCAA), with a standard amino acid solution containing 30% BCAA, on respiration and apnea in premature infants."	Neonate	10	"The routine TPN containing 30% BCAA was prepared with the use of nitrogen, amino acids, and protein (TrophAmine 6%, Kendall McGaw Laboratories, Inc., Irvine, CA) contained the following proportions of amino acids: L-Valine 8%, L-Leucine 14%, L-Isoleucine 8%, L-Lysine 8%, L-Methionine 3%, L-Phenylalanine 5%, L-Threonine 4%, L-Tryptophan 2%, L-Cysteine <0.1%, L-Histidine 5%, L-Tyrosine 2%, L-Alanine 5%, L-Arginine 12%, L-Proline 7%, L-Serine 4%, Glycine 4%, L-Aspartic acid 3%, L-Glutamic acid 5%, and L-Taurine <0.1%. The second TPN solution was prepared with the same total amino acid content but enriched to 53% of the protein as BCAA. The BCAA enriched solution was prepared by mixing 100 mL of 6% TrophAmine with 75 mL of isoleucine, leucine, valine, and phosphate (BranchAmin 4%, Clintec Nutrition Company, Deerfield, IL) to produce a solution containing 5.14% amino acids. This formulation increases the amount of isoleucine and valine by 100% and leucine by 50% as a percentage of total amino acid intake."	In the first 24 h period the routine TPN was administered, in the second 24 h period, TPN with enriched BCAA was administered, and in the last 24 h the initial TPN solution was again administered. Solution was infused although rate was unspecified.	72 hours

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Table 2 (Continued)

ID	Investigator	Publication	Purpose of Study	Age of Subjects	Number of Patients	Formulation/ IV Dosage	Dosage and Administration	Duration
2	Goulet O, DePotter S, et al.	Am J Physiol 265:E540-6, 1993	"The present study used [^{13}C] leucine infusion to assess the response of whole body leucine metabolism to variation in PN (parenteral nutrition) AA (amino acids) intake in children on long-term home cyclic PN."	Child, adolescent	6	"Nitrogen intake was from crystalline L-AA solution (Primene 10%; Cernep Synthelabo, Paris, France) containing 10 g leucine/100 g AA and represented 1.68±0.25 g AA nitrogen per kg/LBM (lean body weight)/day."	". . three levels of AA (0.7, 1.5, 2.5 g per kg/LBM/day) were administered intravenously during three consecutive periods of 7 days each. Order of administration was randomized."	three weeks
3	Rivera A, Jr., Bell EF, et al.	Pediatr Res 33(2):106-11, 1993	". . . to provide information on the safety and efficacy of i.v. administration of crystalline amino acids to low birth weight infants during the first 3 d of life, we determined leucine kinetics, nitrogen balance, and various other biochemical indices in these infants."	Neonate	23	amino acids (Aminosyn PF, Abbott Laboratories, North Chicago, IL) with a cysteine hydrochloride additive (Cysteine Hydrochloride Injection, Abbott Laboratories) "This cysteine additive was omitted inadvertently from the nutrient solutions administered to the first four infants assigned to receive glucose and amino acids. The subsequent seven patients received the amino acid solution plus the cysteine additive (0.5 g cysteine hydrochloride monohydrate/ 12.5 g of other amino acids)."	"Nutrient solutions were infused iv with the use of mechanical pumps. The amino acids were administered at a rate of 1.5 g/kg/day, glucose solution was administered according to the orders of the attending physician.	"The amino acid infusions were started at a mean age of 15 h" and continued until the third day of life.
6	Chin SE, Shepherd RW, et al.	Am J Clin Nutr 56(1):158-63, 1992	"We present the findings of a randomized crossover trial comparing a BCAA (branched chain amino acids)-	Infant, child	19	"Formula 1 is a standard whey-based semi-elemental nutritionally complete formulation (Alfare, Nestle, Vevey, Switzerland) with 21% of the total protein as BCAAs, slightly modified with added maltodextrin (Polyjoule, Sharpe Laboratories Pty Ltd, Erimington, Australia) to provide 1	85-100 ml/kg per day depending on the patients age	8 weeks

Table 2 (Continued)

ID	Investigator	Publication	Purpose of Study	Age of Subjects	Number of Patients	Formulation/ IV Dosage	Dosage and Administration	Duration
6	(cont.)		enriched formulation with an isoenergentic, isonitrogenous standard enteral formulation in children with ESLD (endstage liver disease), using clinical, anthropometric, and body-composition methodology."			kcal/ml and 31 g protein per L." Fat (g/L): 44 (50% MCT oil, 30% milk fat, 20% corn oil) Carbohydrate (g/L): 110 (91% maltodextrin, 8% potato starch, <1% lactose) Protein (g/L): 31 (80% peptides, 20% free amino acids) Branched-chain amino acids(G/L): Leucine: 3.3, Isoleucine: 2.3, Valine: 2.2 Aromatic amino acids (g/L): Phenylalanine: 1.1, Tyrosine: 1.0 "Formula 2 is a modular formulation with equal carbohydrate and long-medium-chain fat contents, containing a BCAA-enriched nutritional supplement (Generaide, Scientific Hospital Supplies, Liverpool, UK) with 31% of the total protein as BCAA (148% of the BCAA content with 175% of the leucine and 164% of the valine content of Formula 1), and administered again to provide 1 kcal/ml and 31 g protein/L." Fat (g/L): 44 (50% MCT oil, 50% safflower oil) Carbohydrate (g/L): 110 (100% maltodextrin) Protein (g/L): 31 (70% peptides, 30% free amino acids) Branched-chain amino acids (g/L): Leucine: 5.8, Isoleucine: 2.3, Valine: 3.6 Aromatic amino acids (g/L): Phenylalanine: 1.4, Tyrosine: 1.3.		

Table 2 (Continued)

ID	Investigator	Publication	Purpose of Study	Age of Subjects	Number of Patients	Formulation/ IV Dosage	Dosage and Administration	Duration
7	Maldonado J, Gil A, et al.	JPEN 13(Jan-Feb):41-6, 1989	"This study was designed to evaluate the effects of two different amino acid PN (parenteral nutrition) solutions, one of them with a high content of BCAA (branched-chain amino acid), on the serum amino acid profiles for both septic and trauma children."	Infant, child	66	FreAmine II (g/16g N): Isoleucine 7.26, Leucine 9.47, Valine 6.89, Methionine 5.54, Cystine 0.20, Phenylalanine 5.90, Tryptophan 1.60, Alanine 7.38, Glycine 14.64, Serine 6.15, Threonine 4.18, Proline 11.69, Lysine 7.63, Histidine 2.96, and Arginine 9.96. F080 (g/16 g N): Isoleucine 11.79, Leucine 14.41, Valine 11.00, Methionine 1.31, Cystine 0.36, Phenylalanine 1.31, Tryptophan 1.00, Alanine 9.83, Glycine 11.79, Serine 6.55, Threonine 5.90. Proline 10.48, Lysine 7.96, Histidine 3.14, and Arginine 7.86.	"Amino acids supply started with 1.5 g/kg/day and increased up to 3 g/kg/day on day 3. The fixed schedule for amino acids was: the first day children received 1.5 g/kg/day, the second day 2.0, and the third day 3.0 g/kg/day; this supply was maintained afterward. The achieved supply of amino acids oscillated in the day 5 between 2.7 and 3.0 g/kg/day."	5 days
8	Imura K, Okada A, et al.	JPEN 12(Sep-Oct):496-504, 1988	"These amino acid solutions prepared by us are characterized by having about 40% of branched-chain amino acids (BCAA), increased arginine (Arg) and decreased glycine (Gly), phenylalanine (Phe), and methionine (Met) as compared with commercially available solutions. In this report, we	Neonate	97	Group PF-I - (mg/dl): Trp 120, Ile 800, Leu 1600, Val 800, Lys 480, Met 60, Phe 400, Thr 240, Arg 1000, His 200, Gly 400, Ala 400, Glu 50, Asp 50, Pro 200, Ser 400, Tyr 50, and CySH 100. Group PF-II - (mg/dl): Trp 120, Ile 800, Leu 1600, Val 800, Lys 480, Met 100, Phe 300, Thr 240, Arg 1000, His 200, Gly 400, Ala 500, Glu 50, Asp 50 Pro 200, Ser 400, Tyr 50, CySH 100. Group PH-III (mg/dl): Trp 120, Ile 800, Leu 1600, Val 600, Lys 480, Met 150, Phe 200, Thr 240, Arg 1000, His 260, Gly 400, Ala 600, Glu 80, Asp 80, Pro 400, Ser 400, Tyr 80, CySH 100. Group MPF (mg/dl): Trp	1.7 to 3.0 g/kg/day of amino acids	Post-operatively

Table 2 (Continued)

ID	Investigator	Publication	Purpose of Study	Age of Subjects	Number of Patients	Formulation/ IV Dosage	Dosage and Administration	Duration
8	(cont.)		infused these amino acid solutions to newborn infants receiving TPN postoperatively, examined the plasma aminograms to compare the dosage of amino acid given with the plasma amino acid profile (dose-response curve), and assessed for nutritional effect in surgical neonates by evaluating nitrogen (N) balance and urinary 3-methyl histidine (3-Mehis) excretion."			Leu 938, Val 338, Lys 660, Met 263, 98, Ile 420, Phe 701, Thr 483, Arg 593, His 450, Gly 803, Ala 465, Glu 488, Asp 285, Pro 248, Ser 165, Tyr 26, CySH 75.		
10	Lucas A, Baker BA, et al.	Arch Dis Child. 68: 579-83, 1993	"We have studied plasma phenyl-alanine concentrations in the early weeks after birth in 336 intensively monitored preterm infants (including) assessments at 18 months post-term. These data have been used to derive reference	Neonate	336	concentration of Vamin 9 was unspecified	unspecified	approximately 10 days

Table 2 (Continued)

ID	Investigator	Publication	Purpose of Study	Age of Subjects	Number of Patients	Formulation/ IV Dosage	Dosage and Administration	Duration
10	(cont.)		concentrations for plasma phenyl-alanine, to quantify the prevalence and severity of hyper-phenylalaninaemia in infants fed intra-venously with Vamin 9 (Kabi), to explore the relation of increased plasma phenylalanine with later developmental scores, and to examine whether attention to the design of intravenous feeding regimens, notably the total energy to protein energy (TE:PE) ratio, could minimize disturbances in plasma concentrations of this amino acid."					
11	Adamkin DH, McClead RE, Jr., et al.	J Perinatol 11(4):375-82, 1991	"The objectives of this multicenter study of preterm infants receiving either TrophAmine or Aminosyn-PF were (1) to evaluate growth and nitrogen balance	Neonate	44	Aminosyn-PF (mg/2.5 g): Essential amino acids: Cysteine 0, Histidine 78, Isoleucine 191, Leucine 297, Lysine 170, Methionine 45, Phenylalanine 107, Threonine 128, Tyrosine 16, N-acetyl-L-tyrosine 0, Tryptophan 45, Valine 161. Nonessential amino acids: Alanine 175, Arginine 307, Aspartic acid 132,	Aminosyn-PF: 2.56±0.04 g/kg/day TrophAmine: 2.66±0.08 g/kg/day	Aminosyn-PF:9.4±0.84 days Trophamine: 9.3±0.88 days

Table 2 (Continued)

ID	Investigator	Publication	Purpose of Study	Age of Subjects	Number of Patients	Formulation/ IV Dosage	Dosage and Administration	Duration
11	(cont.)		and retention; (2) to identify differences (if any) in the resulting plasma aminograms; and (3) to determine the clinical significance of any differences that might be identified."			Glutamic acid 206, Glycine 96, Proline 204, Serine 124, Taurine 18. TrophAmine (mg/2.5g): Essential amino acids: Cysteine HCl-H(2)O 8, Histidine 120, Isoleucine 204, Leucine 349, Lysine 204, Methionine 83, Phenylalanine 120, Threonine 104, Tyrosine 16, N-acetyl-L-tyrosine 42, Tryptophan 50, Valine 195. Nonessential amino acids: Alanine 133, Arginine 304, Aspartic acid 79, Glutamic acid 125, Glycine 92, Proline 170, Serine 96, Taurine 6.		
14	Beck R	Am J Perinatol 7(1):84-6, 1990	"The purpose of this retrospective study was to define the frequency and spectrum of PN-associated direct bilirubinemia in a large population of ELBW (extremely low birthweight) neonates exposed to a PN (parenteral nutrition) regimen containing Troph-amine. A popu-lation of ELBW neonates was specifically selected for review because these infants, by virtue of their prematurity-related	Neonate	35	"All neonates received a PN regimen consisting of Trophamine 6% mixed with dextrose, electrolytes, vitamins (Pediatric MVI, Armour, Kankakee, IL, 0.5 cc/100 cc PN solution) and trace minerals (Neotrace-4, Lyphomed, Rosemont, IL 0.26 cc/kg/day)." The composition of the pediatric amino acid was not given.	"The aim of PN administration was gradually to provide up to 3.0 gm/kg/day of pediatric amino acid solution and a nonprotein intake of 60 to 120 kcal/kg/day, including up to 3.0 gm/kg/day of lipid emulsion." A daily parenteral amino acid dose of 2.39 gm/kg with a range of 2.14-2.77 and total parenteral amino acid dose of 115.1 gm/kg with a range of 56.5-186.5	47.7, with a range of 23-79 days.

Table 2 (Continued)

ID	Investigator	Publication	Purpose of Study	Age of Subjects	Number of Patients	Formulation/ IV Dosage	Dosage and Administration	Duration
14	(cont.)		medical problems, receive the greatest exposure to PN within NICU (neonate intensive care unit) and normally manifest the greatest frequency of direct bilirubinemia."					
17	Rosenthal M	Early Hum Dev 18(1):37-44, 1988	"Evidence is put forward, based on observations reported previously (Rosenthal M, 1987) from a study comparing a current standard amino acid solution for neonates in the U.K., Vamin (Kabivitrum, Sweden) with a new amino acid solution, Paedmin Pfrimmer, F.R.G.) suggesting that urinary amino acid fractional excretion may have a role in neonatal weight gain during TPN."	Neonate	32	Vamin (percent content in TPN solution): Glutamic acid 11.1, Isoleucine 5.4, Leucine 7.3, Methionine 2.4, Phenylalanine 6.0, Tryptophan 0.9, Tyrosine 0.5, Valine 6.5, Cysteine 2.2, Arginine 3.2, Alanine 6.0, Aspartic acid 5.6, Glycine 5.1, Histidine 2.7, Lysine 4.9, Proline 12.7, Serine 12.9, Threonine 4.5. Paedmin (percent content in TPN solution): Glutamic acid 15.3, Isoleucine 4.5, Leucine 5.0, Methionine 1.6, Phenylalanine 2.6, Tryptophan 0.7, Tyrosine 0.4, Valine 4.2, Cysteine 0.4, Arginine 4.7, Alanine 24.6, Aspartic acid 7.3, Glycine 12.3, Histidine 1.1, Lysine 3.3, Proline 8.7, Serine 0.0, Threonine 3.3	2.5 g protein/kg per day from day 1 of TPN	12 to 19 days
18	Heird, WC, Hay W et al	Pediatrics 81(4):41-50, 1988	"The study reported here was designed to evaluate the appropriateness of	Neonate	28	Trophamine (mg/2.5 g of mixture): L-Cysteine 126 (includes 121 mg of L-cysteine added separately when infusate was prepared), L-Histidine	2.5 g/kg/d	5 to 21 days

Table 2 (Continued)

ID	Investigator	Publication	Purpose of Study	Age of Subjects	Number of Patients	Formulation/ IV Dosage	Dosage and Administration	Duration
18	(cont.)		this new parenteral amino acid mixture (Trophamine, Kendall McGaw Laboratories) for LBW (low birth weight) infants requiring parenteral nutrition. The results also provided considerable insight into the LBW infant's ability to use parenterally administered amino acids." "The overall aim of the study was to evaluate the efficacy of Trophamine as the nitrogen source of parenteral nutrition regimens commonly administered to LBW infants."			114, L-Isoleucine 195, L-Leucine 333, L-Lysine 195, L-Methionine 81, L-Phenylalanine 114, L-Threonine 100, L-Tryptophan 48, L-Tyrosine 57 (includes 17 mg of tyrosine plus 40 mg of tyrosine as N-acetyl-L-tyrosine), L-Valine 185, L-Alanine 128, L-Arginine 290, Aspartic acid 76, L-Glutamic acid 119, Glycine 86, L-Proline 162, L-Serine 90, Taurine 6.		

Table 2 (Continued)

ID	Investigator	Publication	Purpose of Study	Age of Subjects	Number of Patients	Formulation/ IV Dosage	Dosage and Administration	Duration
19	Heird WC, Dell RB, et al	Pediatrics 80(3):401-8, 1987	To provide information on the clinical, nutritional, and biochemical effects of a total parenteral nutrition regimen in infants and children.	Neonate, infant, child	40	Trophamine (mg/2.5 g): N-acetyl-L-tyrosine 40, L-Cysteine 126 (includes 121 mg of L-cysteine hydrochloride, added separately when infusate was prepared), L-Histidine 114, L-Isoleucine 195, L-Leucine 333, L-Lysine 195, L-Methionine 81, L-Phenylalanine 114, L-Threonine 100, L-Tryptophan 48, L-Tyrosine 17, L-Valine 185, L-Alanine 128, L-Arginine 290, L-Aspartic acid 76, L-Glutamic acid 119, Glycine 86, L-Proline 162, L-Serine 90, Taurine 6.	2.5 g/kg/d	"The study consisted of three phases: An equilibration period ranging from three to five days (phase 1) during which the children received the desired intake of amino acids (2.5 g/kg/d) with increasing amounts of glucose, as determined by each subject's glucose tolerance, up to a total glucose dosage of 27 g/kg/d (92 kcal/kg/d); a study period of at least five and up to 21 days (phase 2) during which the children received a parenteral nutrition regimen

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Table 2 (Continued)

ID	Investigator	Publication	Purpose of Study	Age of Subjects	Number of Patients	Formulation/ IV Dosage	Dosage and Administration	Duration
19	(cont.)							designed to provide the desired amino acid intake and total nonprotein energy intake of 125 kcal/kg/d (including 3 g/kg/d of a parenteral lipid emulsion); and a post-study period of 48 to 72 hours (phase 3) during which the children received another parenteral amino acid mixture with or without enteral intake depending upon the individual's tolerance of enteral intake. Phase 1 was omitted in patients who were receiving parenteral nutrition at the time of enrollment (n=18). Phase 2 of the study (i.e., the period of full amino acid and energy intake) was divided into five-to-seven-day segments."

Table 2 (Continued)

ID	Investigator	Publication	Purpose of Study	Age of Subjects	Number of Patients	Formulation/ IV Dosage	Dosage and Administration	Duration
21	Coran AG and Drongowski MS	JPEN 11(4):368-377, 1987	"The purpose of this study was to compare the toxicity and efficacy of Neopham (Kabi-Vitrum, Inc.) with Aminosyn (Abbott Laboratories) as a nitrogen source in a TPN (total parenteral nutrition) protocol in infants and children."	Infant, child	24	Neopham (g/dl amino acids): L-isoleucine 0.31, L-leucine 0.70, L-lysine 0.56, L-methionine 0.13, L-phenylalanine 0.27, L-threonine 0.36, L-tryptophan 0.14, L-valine 0.36, L-Histidine 0.21, L-arginine 0.41, L-alanine 0.63, L-proline 0.56, L-serine 0.38, L-tyrosine 0.05, glycine 0.21, L-aspartic acid 0.41, L-glutamic acid 0.71, L-cysteine-cystine 0.10 Aminosyn (g/dl amino acids): L-isoleucine 0.51, L-leucine 0.66, L-lysine 0.51, L-methionine 0.25, L-phenylalanine 0.31, L-threonine 0.37, L-tryptophan 0.12, L-valine 0.56, L-histidine 0.21, L-arginine 0.69, L-alanine 0.90, L-proline 0.61, L-serine 0.30, L-tyrosine 0.04, glycine 0.90, The solutions for centrally administered TPN consisted of 25% glucose and 3.5% crystalline amino acids, while the peripheral regimen consisted of 12.5% glucose and 2.5% crystalline amino acids. The TPN solutions also contained routine vitamin and mineral additives."	The group 1 (Aminosyn) patients received 56.8±8.7 kcal/kg/day of dextrose, 24.6±9.2 kcal/kg/day of Intralipid and 11.7±3.4 kcal/kg/day of amino acids in comparison with the group 2 (Neopham) patients who received 57.6±8.5 kcal/kg/day of dextrose, 23.7±11.3 kcal/kg/day of Intralipid and 11.3±3.3 kcal/kg/day of amino acids The group 1 infants received an average of 2.92 g/kg/day of Aminosyn, while the group 2 infants received 2.84 g/kg/day of Neopham.	"Data from the first 15 days of TPN formed the basis of this study."
22	Pomeranz S, Gimmon Z, et al	JPEN 11(3): 314-315, 1987	Case report of anaphylactic reaction	Child	1	2.75% Travasol® injection , 10% dextrose	solution administered 15 minutes until onset of anaphylaxis	15 minutes
23	Pineault M, Chessex P, et al.	JPEN 11(3): 296-9, 1986	"Elevated glycinemia and glycinuria were reported in patients receiving Travasol® (Travenol-Baxter	Neonate	10	Travasol® 10% blend C amino acids (mmol/L); Isoleucine 45.7, Leucine 55.6, Valine 49.5, Phenylalanine 33.9, Methionine 26.8, Threonine 35,2, Tryptophan 8.8, Lysine 39.6, Histidine 30.9, Tyrosine 2.2,	"The infants received a constant peripheral intravenous infusion of amino acids (2.61±0.02 g/kg/day), fat emulsion (2.0±0.1	4.6±0.3 d

Table 2 (Continued)

ID	Investigator	Publication	Purpose of Study	Age of Subjects	Number of Patients	Formulation/ IV Dosage	Dosage and Administration	Duration
23	(cont.)		Laboratories, Malton, Ontario, Canada) 10% blend B (Chessex P, et al. 1985). The amino acid profile of this solution has been modified into a new solution, blend C. This study was designed to evaluate whether the modifications brought to the new solution Travasol® 10% blend C are of significance for the VLBW (very low birth weight) infant requiring TPN."			Cysteine 0, Alanine 232.3, Arginine 66.0, Aspartate 0, Glutamate 0, Glycine 137.2, Proline 59.1, Serine 47.5	g/kg/day), and dextrose (12.8±0.1 g/kg/day) for 4.6±0.3 days before blood sampling."	
25	Sankaran K, Berscheid B, et al	JPEN 9(4):439-42, 1985	Total parenteral nutrition (TPN) was used in 75 preterm infants with gestational ages less than 32 wk lasting more than 20 days. "Two synthetic amino acid preparations were used as protein base, Aminosyn (Abbott) and Vamin (Pharmacia), during this period. It was our intention	Neonate	75	"Aminosyn was used in a 5 and 10% dextrose solution at concentrations of 1.5 and 3%. Vamin was also used in 1.5 and 3% concentrations in 5 and 10% dextrose." 3% Aminosyn (mg per 100 ml): L-Isoleucine 180, L-Leucine 235, L-Lysine 180, L-Methionine 100, L-Phenylalanine 100, L-Threonine 180, L-Tryptophan 40, L-Valine 200, L-Alanine 320, L-Arginine 245, L-Histidine 75, L-Proline 215, L-Serine 105, L-Tyrosine 22, Glycine 320 3% Vamin (mg per 100 ml) L-Isoleucine 167.7, L-Leucine 294.1,	Aminosyn 3.2±1.7 g/kg/day; Vamin 2.9±2.1 g/kg/day	Aminosyn 35.3±5 days; Vamin 39.7±4 days

Table 2 (Continued)

ID	Investigator	Publication	Purpose of Study	Age of Subjects	Number of Patients	Formulation/ IV Dosage	Dosage and Administration	Duration
25	(cont.)		to assess the clinical and metabolic effects of these two preparations in these critically ill preterm infants with gestation < 32 wk."			L-Lysine 167.7, L-Methionine 81.7, L-Phenylalanine 236.5, L-Threonine 129.0, L-Tryptophan 43.0, L-Valine 184.9, L-Alanine 129.0, L-Arginine 141.9, L-Histidine 103.2, L-Proline 348.3, L-Serine 322.5, L-Tyrosine 21.5, Glycine 90.3, L-Aspartic acid 176.3, L-Cysteine/L-cystine 60.2, L-Glutamic acid 387.0		
27	Chessex P, Zebiche, H, et al	Pediatrics 106(1):111-7, 1985	To compare under similar conditions the effects of two crystalline amino acid solutions on the nitrogen retention and plasma amino acid levels of very small preterm infants receiving both solutions	Neonate	15	Travasol® 10% blend B (0.167 g nitrogen for each g of amino acid) Vamin 7% (0.134 g of nitrogen for each g amino acid)	"An amino acid intake (continuous infusion) providing 450 mg/kg/day nitrogen was prescribed in an attempt to duplicate an intrauterine nitrogen retention of approximately 300 mg/kg/day (Zlotkin SH, et al. 1981)	"Each infant was studied twice in a crossover design while receiving, over two consecutive periods of 6 days, two infusion regimens differing only by the quality of the amino acids infused."
28	Shohat M, Wielunsky E, et al	JPEN 8(2):178-80, 1984	"Total parenteral nutrition (TPN) with solutions containing protein hydrolysate as a nitrogen source may result in hyperammonemia (Johnson JD, et al. 1972). This complication has	Neonate	44	"The concentration of protein (as amino acids) ranged from 2-3 g/100 ml as crystalline synthetic L amino acid (Travasol®) . . ."	the total daily intake of protein averaged 2.2 g/kg/day. Protein intake was reduced to 1 g/kg/day whenever plasma ammonia levels were above 200 ug/100 ml."	5 to 42 days

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Table 2 (Continued)

ID	Investigator	Publication	Purpose of Study	Age of Subjects	Number of Patients	Formulation/ IV Dosage	Dosage and Administration	Duration
28	(cont.)		been observed in infants receiving TPN with synthetic L-amino acid (Freeamine) and could be corrected or prevented by the administration of arginine (Heird WC, et al. 1972). Therefore, as new commercial preparations containing high arginine concentration became available, it was expected that hyperammonemia could be prevented. Indeed, in infants and children, significant hyperammonemia has not been observed with this solution (O'Neill JA, et al. 1976)." "In order to test this hypothesis in preterm infants we prospectively studied the incidence and severity of hyperammonemia in infants with birth weight less than					

Table 2 (Continued)

ID	Investigator	Publication	Purpose of Study	Age of Subjects	Number of Patients	Formulation/ IV Dosage	Dosage and Administration	Duration
28	(cont.)		1800 g receiving TPN, with such a synthetic amino acid solution as the nitrogen source (Travasol-Travenol Ashdod, Israel)."					
29	Vanderhoof JA and Antonson DA	Acta Chir Scand Suppl 517:69-78, 1983	"The purpose of this study was to compare safety and efficacy of N (Neopham, Cutter Laboratories, Berkeley, CA) versus T(Travasol, Baxter Travenol, Deerfield, IL) in short term central TPN in infants and to evaluate changes in serum amino acid levels in infants receiving N versus T."	Neonate	12	Neopham (percent concentrations of amino acids) Isoleucine 4.8, Leucine 10.8, Lysine 8.6, Methionine 2.0, Phenylalanine 4.2, Threonine 5.5, Tryptophan 2.2, Valine 5.5, Histidine 3.2, Tyrosine 0.8, Cysteine 1.5, Alanine 9.7, Proline 8.6, Arginine 6.3, Serine 5.8, Glycine 3.2, Aspartic acid 6.3, Glutamic acid 10.9, Travasol® (percent concentrations of amino acids) Isoleucine 4.8, Leucine 6.2, Lysine 5.8, Methionine 5.8, Phenylalanine 6.2, Threonine 4.2, Tryptophan 1.8, Valine 4.6, Histidine 4.4, Tyrosine 0.4, Cysteine 0, Alanine 20.7, Proline 4.2, Arginine 10.4, Serine 0, Glycine 20.7, Aspartic acid 0, Glutamic acid 0	"The final infusion rate ranged from 100 to 130 mL/kg/day, based upon the child's calculated caloric requirement and clinical response to the parenteral nutrition."	"T(ravasol) patients were maintained on the protocol for a mean of 11 days, N(eopham) patients for a mean of 12 days. All patients were on the study for at least 8 days."
30	Coran A, Drongowski R, et al	Acta Chir Scand Suppl 517:57-68, 1983	"The purpose of this study was to compare the safety and efficacy of Neopham (Cutter Laboratories, Berkeley, CA) with Aminosyn (Abbott Laboratories, Chicago, IL) as a nitrogen source in	Neonate, infant, child	17	Neopham (g/dl amino acids): L-isoleucine 0.31, L-leucine 0.70, L-lysine 0.56, L-methionine 0.13, L-phenylalanine 0.27, L-threonine 0.36, L-tryptophan 0.14, L-valine 0.36, L-histidine 0.21, L-arginine 0.41, L-alanine 0.63, L-proline 0.56, L-serine 0.38, L-tyrosine 0.05, glycine 0.21, L-aspartic acid 0.41, L-glutamic acid 0.71, L-cysteine-cystine 0.10	continuous infusion	a minimum of 7 days

Table 2 (Continued)

ID	Investigator	Publication	Purpose of Study	Age of Subjects	Number of Patients	Formulation/ IV Dosage	Dosage and Administration	Duration
30	(cont.)		TPN protocols in infants and children."			Aminosyn (g/dl amino acids): L-isoleucine 0.51, L-leucine 0.66, L-lysine 0.51, L-methionine 0.28, L-phenylalanine 0.31, L-threonine 0.37, L-tryptophan 0.12, L-valine 0.56, L-histidine 0.21, L-arginine 0.69, L-alanine 0.90, L-proline 0.61, L-serine 0.30, L-tyrosine 0.04, glycine 0.90, "The solution for centrally-administered TPN consisted of 25% glucose and 3.5% crystalline amino acid, while the peripheral regimen consisted of 12.5% glucose and 2.5% crystalline amino acids. The TPN solutions also contained routine vitamin and mineral additives."		
31	Chase HP and Nixt TL	Acta Chir Scand Suppl 517:49-56, 1983	". . . a double-blind study comparing the effects in infants of Neopham amino acids solution (N, Cutter Laboratories, Berkeley, CA) with FreAmine III (F, McGaw Laboratories, Irvine, CA) . . . "	Infant	11	Neopham (N) amino acid composition (%): Isoleucine 4.8, Leucine 10.8, Lysine 8.6, Methionine 2.0, Phenylalanine 4.2, Threonine 5.5, Tryptophan 2.2, Valine 5.5, Alanine 9.7, Proline 8.6, Histidine 3.2, Arginine 6.3, Serine 5.8, Tyrosine 0.8, Glycine 3.2, Aspartic acid 6.3, Glutamic acid 10.9, Cysteine /Cystine 1.5. FreAmine III (A) amino acidcomposition (%): Isoleucine 7.2, Leucine 9.3, Lysine 7.5, Methionine 5.4, Phenylalanine 5.8, Threonine 4.1, Tryptophan 1.6, Valine 6.8, Alanine 7.3, Proline 11.5, Histidine 2.9, Arginine 9.8, Serine 6.1, Tyrosine 0, Glycine 14.4, Aspartic acid 0, Glutamic acid 0, Cysteine/Cystine <0.2 "All the infants	Intravenously at a concentration of 2 g/100 mL	"All infants were to receive the intravenous solutions for a minimum of one week, although some received them much longer."

Table 2 (Continued)

ID	Investigator	Publication	Purpose of Study	Age of Subjects	Number of Patients	Formulation/ IV Dosage	Dosage and Administration	Duration
31	(cont.)					received 20% dextrose except for one who could not tolerate that concentration."		
32	Ogata ES, Boehm JJ, et al	Acta Chir Scand Suppl 517:39-48, 1983	"To test the effects of (a) new amino acid solution (N, Neopham, Cutter Laboratories, Berkeley, CA), we administered it and a presently available standard amino acid solution Aminosyn (A, Abbott Laboratories, North Chicago, IL), in a randomized prospective trial in premature infants."	Neonate	17	Neopham; amino acid concentrations (%): Isoleucine 4.8, Leucine 10.8, Lysine 8.6, Methionine 2.0, Phenylalanine 4.2, Threonine 5.5, Tryptophan 7.2, Valine 5.5, Histidine 3.2, Tyrosine 0.8, Cysteine 1.5, Alanine 9.7, Proline 8.6, Arginine 6.3, Serine 5.8, Glycine 3.2, Aspartic acid 6.3, Glutamic acid 10.9, Aminosyn; amino acid concentration (%): Isoleucine 7.3, Leucine 9.5, Lysine 7.3, Methionine 4.0, Phenylalanine 4.4, Threonine 5.3, Tryptophan 1.7, Valine 8.0, Histidine 3.0, Tyrosine 0.6, Cysteine 0.0, Alanine 12.9, Proline 8.8, Arginine 9.9, Serine 4.3, Glycine 12.9, Aspartic acid 0.0 , Glutamic acid 0.0 "The concentration of glucose in the TPN solution was initially 75 g/100 mL and was increased to 12 g/100 mL when the infant could maintain a plasma glucose concentration of 150 mg/dl or less."	Neopham: 2.56±0.4 g/kg/day Aminosyn: 2.69±0.4 g/kg/day	2 weeks

Table 2 (Continued)

ID	Investigator	Publication	Purpose of Study	Age of Subjects	Number of Patients	Formulation/ IV Dosage	Dosage and Administration	Duration
33	Seashore JH and Seashore MR et al	JPEN 6(2):114-8, 1982	"This report is a review of our experience with hyperammonemia during TPN (total parenteral nutrition) in infants and children."	Neonate, infant, child, adolescent	52	Amigen (casein hydrolysate), FreAmine II (crystalline amino acid solution) and Travasol® (crystalline amino acid solution)	Amigen and FreAmine II: "Early in this series, a few patients received up to 4.5 g/kg/day of protein. Since 1974, all infants have received a standard 2% protein solution providing 2.5 to 3.0 g/kg/day of protein. Older children received 1.5 to 2.0 g/kg/day of protein." Travasol: 2.5 to 3.0 g/kg/day protein	five to 209 days

Attachment 3

Bibliography of Literature Articles

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Section J: Original References and Study Reports

Study Identifier	Reference Citation
1	Blazer S, Reinersman GT, et al. (1994). Branched-chain amino acids and respiratory pattern and function in the neonate. J-Perinatol. 14(4):290-5
2	Goulet O, DePotter S, et al. (1993). Leucine metabolism at graded amino acid intakes in children receiving parenteral nutrition. Am-J-Physiol. 265(4 Pt 1):E540-6
3	Rivera A, Jr., Bell EF, et al. (1993). Effect of intravenous amino acids on protein metabolism of preterm infants during the first three days of life. Pediatr-Res. 33(2):106-11
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Attachment 6

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