# Evaluation of a New Amino Acid Source for Use in Parenteral Nutrition

MICHAEL D. CALDWELL, M.D.,* JAMES A. O'NEILL, JR., M.D., H. C. MENG, M.D., PH.D., MILDRED H. STAHLMAN, M.D.

*From the Departments of Physiology, Surgery and Pediatrics, Vanderbilt University School of Medicine, Nashville, Tennessee 37232*

**Ninety-two patients, ranging from two days to 92 years of age, received parenteral nutrition using a new synthetic amino acid solution designed to provide optimal nitrogen retention and obviate metabolic complications. Weight gain and positive nitrogen balance were produced in the majority of patients. Hyperchloremic acidosis and hypophosphatemia did not occur. Hyperammonemia in infants was avoided with the exception of occasional, transient, asymptomatic elevations of blood ammonia in low birth weight infants. It was suspected that an inadequate nonprotein calorie/gram of nitrogen ratio may have been employed in these infants. Blood ammonia levels declined from initial levels in 80% of adult patient. Nitrogen retention was directly proportional to the supply of nonprotein calories.**

INTRAVENOUS ADMINISTRATION has become the favored route for parenteral nutrition because large volumes of fluid are necessary to provide required nutrients, and absorption of these nutrients is slow and uncertain by other parenteral means. Constant infusion over 24 hours is required to allow maximum utilization of the large amount of carbohydrate currently used as the main calorie source.

The provision of intravenous nutrients differs from normal digestion and assimilation of foodstuffs in two primary ways: the usual hepatic and gastrointestinal regulatory mechanisms are bypassed; and nutrients are provided constantly rather than as intermittent meals. To compensate for the loss of regulatory mechanisms, parenteral nutrition solutions have been structured to mimic the form in which nutrients are normally absorbed; i.e., carbohydrate is supplied as a monosaccharide, and protein as fibrin or casein hydrolysate or as individual amino acids.

Glucose appears to be a satisfactory energy source. Problems have arisen, however, with a variety of protein sources.[6] If protein hydrolysates are administered intravenously with adequate nonprotein calories, positive nitrogen balance usually results. Patel et al., however, demonstrated that the nitrogen retention obtained with intravenous protein hydrolysates was much less than that achieved in the same patients ingesting equivalent amounts of the whole protein orally.[18] By analysis of blood aminograms, these investigators concluded that a deficiency of aromatic and sulfur-containing amino acids in the protein hydrolysate led to the impaired nitrogen retention. As a consequence of these findings, they proposed an intravenous, synthetic amino acid formulation which provided a nitrogen balance comparable to orally ingested whole meat and egg protein.[1] Although synthetic amino acid solutions previously used for intravenous nutrition have demonstrated effective nitrogen retention, concomitant development of hyperammonemia,[10] hyperchloremic acidosis,[9] and hypophosphatemia[23] occurred. The current studies, therefore, were designed to determine if the new formulation reported by Anderson, Patel and Jeejeebhoy[1] could prove clinically effective while obviating the above metabolic complications.

Submitted for publication April 3, 1976.

* Reprint requests: Michael D. Caldwell, M.D., MAJ, MC, Chief, Division of Surgical Metabolism, Department of Surgery, Letterman Army Institute of Research, Presidio of San Francisco, California 94129.

TABLE 1. *Patient Population*

| General Diagnosis* | No. Patients |
|---|---|
| Malignancy (surgical, radiation and chemotherapy) | 15 |
| Congenital Birth Defects (gastroschisis, omphalocele, intestinal atresia, etc.) | 12 |
| Prematurity (with or without hyaline membrane disease | 9 |
| External Gastrointestinal Fistula | 7 |
| Intestinal Obstruction | 6 |
| Multiple Trauma and Burns | 5 |
| Regional Enteritis | 5 |
| Chronic Diarrhea, Malabsorption | 4 |
| Complicated Peptic Ulcer Disease | 3 |
| Trauma (Duodenal hematoma, small GSW) | 2 |
| Complicated Pancreatitis | 2 |
| Perforated Viscus | 2 |
| Mesenteric Vascular Occlusion | 2 |
| Postoperative Decreased Oral Intake | 2 |

* Patients having a diagnosis falling in more than one group are listed in that group most representative of the indication for parenteral nutrition therapy.

## Materials and Methods

Ninety-two patients received parenteral nutrition during this 18 month study. Sixteen patients received oral nutrient supplementation during the period of parenteral nutrition and therefore were excluded. The age range of the remaining 76 patients was two days postnatal to 92 years. The period of parenteral nutrition therapy varied from 5 to 75 days with a mean of 19.7 days. A list of major diagnoses and number of patients in each group is provided in Table 1. The formulation of the standard parenteral nutrition solutions used is given in Tables 2 and 3. Various components of the solutions were modified as required by the metabolic demands of the individual patient. Solutions were compounded and alterations or additions were made in the hospital pharmacy using aseptic technique under a laminar flow hood.

Solutions in excess of 100 gm/liter of glucose were administered via percutaneous subclavian venous catheterization in adults and open common facial, external or internal jugular catheterization in infants. In every case, the position of the catheter tip was determined roentgenographically and infusion of parenteral nutrition solutions was not begun until it was determined that the catheter tip lay in the superior vena cava.

Initiation of the parenteral nutrition therapy occurred as follows: in adults; 50 ml/hr for the first 24 hours; 85 ml/hr the second 24 hours; 125 ml/hr the third 24 hours. The remaining fluid requirements were given as 5% Dextrose solutions via a peripheral intravenous route. Infants received solutions containing one-half of the standard amounts of glucose and amino acids the first 24 hours; three-quarters the second 24 hours, then the standard amounts thereafter. In both groups, if evidence of glucose intolerance developed, the rate of infusion was slowed, and, if required, regular insulin was added to the solutions until endogenous insulin secretion allowed efficient utilization of the infused glucose.

The following biochemical monitoring schedule was employed: hemoglobin, leukocyte count, hematocrit, and platelet count weekly; BUN, $Na^+$, $K^+$, $Cl^-$, $CO_2$ content and blood glucose at least daily until the patient had been on full strength intravenous nutrient solution for 3 days and then at least every 3 days thereafter; urinary sugar determinations every 6 hours; serum osmolality during periods of significant hyperglycemia; SMA-12, blood ammonia and serum magnesium weekly. Pediatric patients were monitored similarly using micro techniques. All determinations, with the exception of blood ammonia and urinary nitrogen, were made in the Vanderbilt University Hospital clinical laboratories using automated or semi-automated techniques. For ammonia determinations, venous blood samples drawn into heparinized tubes were kept on ice and analyzed, within 30 minutes after sampling, by a modification of the method of Conway.[5] Twenty-four hour urine collections for urinary nitrogen determinations were collected under toluene and on ice. Following collection and recording of 24 hour volume, a well-mixed aliquot was taken and stored at −20° until analysis. The samples were analyzed by the automated method of Catanzaro.[7]

TABLE 2. *Composition of Standard Parenteral Nutrition Solutions*

| Component | Amount per Liter of Final Mixture | |
|---|---|---|
| | Adult | Infant |
| Non-protein calories (as glucose) | 900.0 | 800.0 |
| Nitrogen (gm) (as crystalline amino acids)* | 4.3 | 4.3 |
| Na (meq) | 32.6 | 32.6 |
| K (meq) | 40.0 | 30.0 |
| Cl (meq) | 32.6 | 32.6 |
| Mg (meq) | 10.0 | 10.0 |
| Ca (meq) | 5.0 | 10.0 |
| P (mg) (elemental) | 426.0 | 426.0 |
| $ZnSO_4$ (mg) | 5.0 | 10.0 |
| Acetate (meq) | 78.0 | 62.7 |
| Vitamins† | | |
| C (mg) | 155.0 | 300.0 |
| $B_1$ (mg) | 5.5 | 20.0 |
| $B_2$ (mg) | 1.1 | 4.0 |
| $B_6$ (mg) | 1.7 | 6.0 |
| $B_{12}$ (mg) | 10.0 | 100.0 |
| Niacin (mg) | 11.0 | 40.0 |
| Panthenol (mg) | 2.8 | 10.0 |
| Folic acid (mg) | 100.0 | 1000.0 |
| A (units) | 1100.0 | 4000.0 |
| D (units) | 110.0 | 480.0 |
| E (units) | 0.55 | 2.0 |

* Travasol Injection (Travenol Laboratories, Morton Grove, Illinois).

† Substantial amounts (Adults, 1.1 cc/liter; Infants, 4.0 cc/liter) of vitamins from MVI (Multi-Vitamin Infusion solution), USV Pharmaceutical Corporation.

TABLE 3. *Composition of Amino Acid Injection**

| Amino Acids | Final Solution (gm/l) |
|---|---|
| L-Leucine | 1.59 |
| L-Methionine | 1.49 |
| L-Lysine (HCl salt) | 1.49 |
| L-Isoleucine | 1.23 |
| L-Valine | 1.18 |
| L-Histidine | 1.13 |
| L-Threonine | 1.08 |
| L-Tryptophan | 0.47 |
| L-Alanine | 5.33 |
| Glycine | 5.33 |
| L-Arginine | 2.66 |
| L-Proline | 1.08 |
| L-Tyrosine | 0.10 |
| Total L-Amino Acids | 25.71 |
| Total Nitrogen | 4.30 |
| $\frac{\text{Grams Amino Acids}}{\text{Grams Nitrogen}} =$ | 5.98 |
| **Electrolytes** | **Final Solution (meq/l)** |
| Sodium | 32.6 |
| Potassium | 28.0 |
| Magnesium | 4.7 |
| Chloride | 32.6 |
| Phosphate | 28.0† |
| Acetate | 60 |

* When diluted to degree necessary for preparation of one liter of standard parenteral nutrition.
† 328 mg elemental phosphorus.

For the purpose of these studies, nitrogen balance was considered to represent the difference between the amount of nitrogen infused and the total urinary nitrogen excreted each 24 hours. Since most patients on parenteral nutrition have infrequent stools, the fecal nitrogen loss was considered negligible in this calculation. Any patients with suspected large gastrointestinal nitrogen losses were eliminated from nitrogen balance studies. The relatively small, 5.5 mg/kg, daily obligatory nitrogen loss from the skin and other minor routes[16] was not included in the nitrogen-balance calculations.

## Results

Tables 4 and 5 list the metabolic parameters studied for patients 0–13 and 13–92 years of age, respectively. The tables were derived by taking the average values of each parameter for each patient during 5 day intervals. The values shown represent the mean ± SEM for the 5 day averages of the number of patients listed in parentheses. The cases in which the number of patients listed in parentheses actually exceeds the reported number of patients results from the fact that parenteral therapy was discontinued for prolonged periods in several patients and then restarted. Since the metabolic state of these

TABLE 4. *Children Under 13 Years**

| Parameter (Normal Value) | Days of Therapy 1–5 | 6–10 | 11–15 | 16–20 | 21–25 | 26–30 |
|---|---|---|---|---|---|---|
| 1. Glucose (70–100 mg/dl) Fasting | 114.6 (27) ± 8.3 | 117.1 (27) ± 7.1 | 116.3 (24) ± 8.8 | 106.3 (11) ± 7.4 | 90.3 (5) ± 4.2 | 99.2 (3) ± 26.2 |
| 2. Sodium (136–143 meq/L) | 136.0 (31) ± .2 | 136.6 (30) ± .8 | 136.7 (23) ± .8 | 136.7 (14) ± 1.2 | 137.2 (10) ± 1.0 | 136.0 (2) |
| 3. Potassium (4.1–5.6 meq/L) | 4.7 (30) ± .1 | 4.8 (28) ± .2 | 5.0 (23) ± .1 | 5.0 (13) ± .2 | 5.1 (9) ± .2 | 5.3 (2) |
| 4. Calcium (10–12 mg/dl) | 9.0 (23) ± .3 | 9.1 (12) ± .2 | 9.1 (11) ± .2 | 9.6 (4) ± .2 | 9.3 (4) ± .3 | 10.4 (1) |
| 5. Magnesium (1.3–3.0 mg/dl) | 1.5 (2) | 1.9 (5) ± .1 | 2.2 (3) ± .2 | | 1.9 (1) | 2.0 (1) |
| 6. Total Protein (4.5–7.3 g/dl) | 4.4 (27) ± .2 | 4.8 (18) ± .3 | 5.1 (19) ± .4 | 4.9 (5) ± .5 | 4.4 (6) ± .8 | 5.7 (3) ± .6 |
| 7. B.U.N. (7–17 mg/dl) | 13.5 (27) ± .9 | 14.4 (28) ± 1.1 | 18.2 (21) ± 1.9 | 16.8 (13) ± 2.8 | 14.6 (7) ± 2.4 | 14.2 (3) ± 4.2 |
| 8. Ammonia (90–150 μg/dl) | 126.6 (7) ± 32.8 | 130.0 (3) ± 26.0 | 137.5 (4) ± 19.5 | 163.0 (1) | 104.7 (3) ± 33.8 | |
| 9. Phosphorus (4.0–6.5 mg/dl) | 4.2 (7) ± .6 | 5.1 (3) ± .5 | 5.3 (6) ± .5 | 4.1 (1) | 5.3 (3) ± .7 | 4.6 (2) |
| 10. $CO_2$ Content (20.3–31.5 mm/L) | 27.4 (24) ± 1.0 | 29.1 (23) ± .13 | 28.1 (18) ± 1.2 | 24.3 (11) ± 1.2 | 23.3 (8) ± 1.3 | 32.0 (3) ± 7.1 |
| 11. Chloride (98–106 meq/L) | 100.8 (25) ± 1.5 | 98.0 (24) ± 1.3 | 100.5 (20) ± 1.5 | 102.4 (12) ± 2.0 | 101.3 (5) ± 2.2 | 93.3 (2) |

* Where normal values for children have not been established in our laboratory, values from reference 10 were used.

TABLE 5. *Adults (13–92 Years)*

| Parameter (Normal Value) | Days of Therapy 1–5 | 6–10 | 11–15 | 16–20 | 21–25 | 26–30 |
|---|---|---|---|---|---|---|
| 1. Glucose (80–120 mg/dl) (Fasting) | 172.3 (45) ± 13.4 | 191.8 (37) ± 17.2 | 198.1 (25) ± 31.3 | 187.8 (18) ± 20.3 | 214.4 (5) ± 41.2 | 245.9 (6) ± 47.8 |
| 2. Sodium (135–145 meq/L) | 136.2 (48) ± 0.7 | 135.9 (44) ± .7 | 136.5 (26) ± .8 | 134.2 (19) ± 1.0 | 135.9 (11) ± 1.4 | 137.7 (8) ± 1.3 |
| 3. Potassium (3.5–5.5 meq/L) | 4.2 (51) ± .1 | 4.4 (41) ± .1 | 4.5 (27) ± .1 | 4.5 (17) ± .1 | 4.5 (10) ± .1 | 4.5 (7) ± .2 |
| 4. Calcium (8.5–11.0 mg/dl) | 9.0 (31) ± .1 | 9.1 (22) ± .3 | 8.7 (17) ± .6 | 9.4 (10) ± .1 | 9.9 (4) ± .5 | 10.0 (5) ± .7 |
| 5. Total Protein (6.0–8.0 g/dl) | 6.3 (38) ± .1 | 6.1 (24) ± .2 | 5.0 (16) ± .6 | 5.7 (13) ± .5 | 6.2 (6) ± .5 | 6.3 (5) ± .4 |
| 6. Albumin (3.5–5.5 g/dl) | 3.13 (35) ± .2 | 2.7 (19) ± .2 | 2.7 (14) ± .2 | 2.5 (12) ± .1 | 2.2 (4) ± .3 | 2.5 (6) ± .4 |
| 7. B.U.N. (5–25 mg/dl) | 15.7 (42) ± 1.3 | 18.44 (30) ± 1.8 | 20.0 (22) ± 1.9 | 19.2 (21) ± 1.9 | 21.0 (8) ± 2.3 | 21.0 (5) ± 2.9 |
| 8. Uric Acid (1.5–7.0 mg/dl) | 4.3 (35) ± .3 | 3.1 (19) ± .3 | 3.5 (15) ± .5 | 4.4 (11) ± .7 | 5.7 (4) ± 2.1 | 3.1 (3) ± .3 |
| 9. Ammonia (40–110 μg/dl) | 141.3 (6) ± 9.4 | 165.9 (9) ± 21.6 | 152.0 (5) ± 21.6 | 161.0 (4) ± 20.1 | 148.4 (2) ± 14.8 | 162.7 (3) ± 17.1 |
| 10. Phosphorus (2.5–4.5 mg/dl) | 3.5 (29) ± .2 | 3.8 (22) ± .2 | 3.9 (15) ± .2 | 4.4 (11) ± .3 | 5.7 (2) ± .5 | 3.9 (5) ± .5 |
| 11. $CO_2$ Content (22–32 mm/L) | 30.3 (49) ± .7 | 31.1 (41) ± .7 | 30.7 (26) ± .8 | 30.6 (19) ± 1.3 | 29.8 (10) ± .9 | 28.0 (7) ± 1.4 |
| 12. Chloride (95–110 meq/L) | 96.7 (46) ± .8 | 95.9 (41) ± .9 | 94.2 (28) ± 1.2 | 94.2 (19) ± 1.6 | 94.2 (11) ± 1.7 | 97.6 (6) ± 3.0 |

patients was different during the two separate periods of study, the data were grouped separately.

### *0 to 13 Year Age Group*

The 31 children who underwent parenteral nutrition during the period of study tolerated the infusions well (Table 4). Serum sodium, potassium, and blood urea nitrogen remained in the normal range throughout the continuous infusions. Blood glucose was maintained at a slightly elevated level. The values not only represent the state of glucose utilization in these patients but also the result of exogenous intervention to maintain normoglycemia. Glucosuria was generally observed only in small premature infants or during periods of stress in full term infants and children. Persistent glucosuria was corrected by slowing the infusion rate or by adding regular insulin (1 unit/20–25 gm glucose) to the nutrient solution. In addition, alteration of the solutions to include fructose up to 50% of the total carbohydrate content decreased glucosuria in premature neonates under 1500 gm body weight.

The serum calcium was low throughout the length of infusions, however, serum ionized calcium remained at approximately 53% of total calcium as determined by Gardner's modification of the McLean-Hastings nomogram.[17] The Ca × P product rose from an initial mean value of 33.8 to a normal value of about 50 mg/dl[8] by the end of the first week of intravenous nutrition. These findings, plus the concomitant demonstration of consistently normal serum phosphorus, suggest the amounts of calcium and phosphorus included in the intravenous nutrient solutions were adequate. It should be noted, however, that the calcium/phosphorus ratio in the infant intravenous formulation is 0.47 rather than the suggested ratio of 1–2.[8]

The few serum magnesium and albumin concentrations measured were normal. Total protein concentrations remained in the low normal range and this is possibly a manifestation of immaturity and/or severe stress on hepatic protein synthesis. However, these patients were generally in positive nitrogen balance after the first week of intravenous nutrition and, in the 21 children and infants in whom chronic body weight measurements were possible, the weight gain was 16.3 ± 5.5 gm/day. This weight gain is meaningful when it is considered

TABLE 6. *Selected Liver Function Studies in Patients with No Known Hepapathology*

| Parameter (Normal Value) | Days of Intravenous Nutrition 1–5 | 6–10 | 11–15 | 16–20 |
|---|---|---|---|---|
| LDH (100–255 I.U.) | 233.4 ± 28.3 (19) | 245.0 ± 15.8 (9) | 225.4 ± 16.7 (7) | 206.5 ± 38.4 (6) |
| Total Bilirubin (0.15–1.00 mg/dl) | 1.2 ± 0.2 (14) | 1.2 ± 0.3 (9) | 1.3 ± 0.3 (6) | 1.03 ± 0.2 (6) |
| Alkaline Phosphatase (30–105 I.U.) | 35.0 ± 9.1 (14) | 85.1 ± 29.6 (9) | 50.5 ± 26.1 (6) | 30.1 ± 13.0 (4) |
| Known Hepatopathology | | | | |
| LDH | 408.6 ± 80.8 (16) | 310.8 ± 40.8 (10) | 357.8 ± 48.0 (8) | 270.7 ± 43.3 (5) |
| Total Bilirubin | 6.0 ± 1.5 (18) | 7.7 ± 2.6 (12) | 7.7 ± 2.2 (10) | 9.0 ± 3.6 (8) |
| Alkaline Phosphatase | 55.0 ± 17.8 (18) | 29.9 ± 6.0 (10) | 36.1 ± 6.0 (10) | 44.8 ± 11.8 (8) |
| S.G.O.T. (0–40 I.U.) | 183.4 ± 62.2 (17) | 151.2 ± 44.7 (9) | 143.1 ± 37.7 (10) | 104.8 ± 44.5 (8) |

that the disease processes in 30% of these children can be taken to be "hypercatabolic" (immediately postoperative, servere trauma, malignancy, etc.).

As can be seen from Table 4, the serum carbon dioxide content and chloride values remained normal for children. There was no evidence of hyperchloremic metabolic acidosis similar to that reported by Heird et al. in association with the use of other synthetic amino acid mixtures.[9]

The values for blood ammonia were within the normal limits for infants and children of this age group except for occasional single determinations. There was no evidence of sustained elevated serum ammonia levels and the occasional elevated levels were asymptomatic.* This was in contrast to studies with other synthetic amino acid solutions where symptomatic hyperammonemia has been reported.[10]

*13 to 92 Year Age Group (Table 5)*

Only the values for blood glucose, ammonia, and serum albumin deviated from the normal range in the 45 adult patients. The blood glucose values presented in Table 5, although significantly above fasting levels, reflect the constant infusion of 25% glucose solutions. In most patients, the blood glucose remained at or below 200 mg/dl without the addition of insulin to the intravenous nutrient solutions. However, in severely stressed patients or in those with overt or latent diabetes mellitus, insulin was required to prevent hyperglycemia, excessive glycosuria and resultant hyperosmolar complications.

For the purpose of determining the effect of the amino acid solution on blood ammonia levels in the adult patients, the time of initial blood ammonia determination was designated as the first day of treatment (Table 5). All of the adult patients had elevated serum ammonia levels at the time of initial measurement. Eighty-five per cent of the initial measurements were made within the first week of parenteral feeding. When the data are examined on an individual patient basis, 80% of those patients showed a decrease in blood ammonia during the period of therapy (mean drop of 24.8%). Only two patients showed an increase in blood ammonia with therapy. A 14% increase was seen in a patient with a hepatic gunshot wound and a 5% increase in a patient with metastatic lymphosarcoma.

Serum sodium and chloride values were at the lower limits of normal while the carbon dioxide content remained at the higher limits of normal in these patients. This tendency toward hypochloremic metabolic alkalosis was thought to represent insufficient provision of sodium chloride to replace prolonged gastrointestinal losses.

TABLE 7. *Nitrogen Balance: gm/kg/day*

| Days | Children | Adults |
|---|---|---|
| 1–5 | +0.13 ± 0.05 (11) | −.0071 ± .0145 (26) |
| 6–10 | +0.21 ± 0.03 (12) | +.0183 ± .0171 (27) |
| 11–15 | +0.24 ± 0.05 (11) | +.0338 ± .0262 (14) |
| 16–20 | +0.12 ± 0.07 (5) | +.0236 ± .0134 (11) |
| 21–25 | +0.23 ± 0.14 (3) | +.0762 ± .0315 (6) |
| 26–30 | | +.0804 ± .0494 (3) |

* Although relatively few blood ammonia levels are reported here, the studies to date have been extended to include 91 infants and children in whom an absence of significant hyperammonemia was found. These data will be published separately (O'Neill, J. A., et al., J. Ped. Surg., in press).

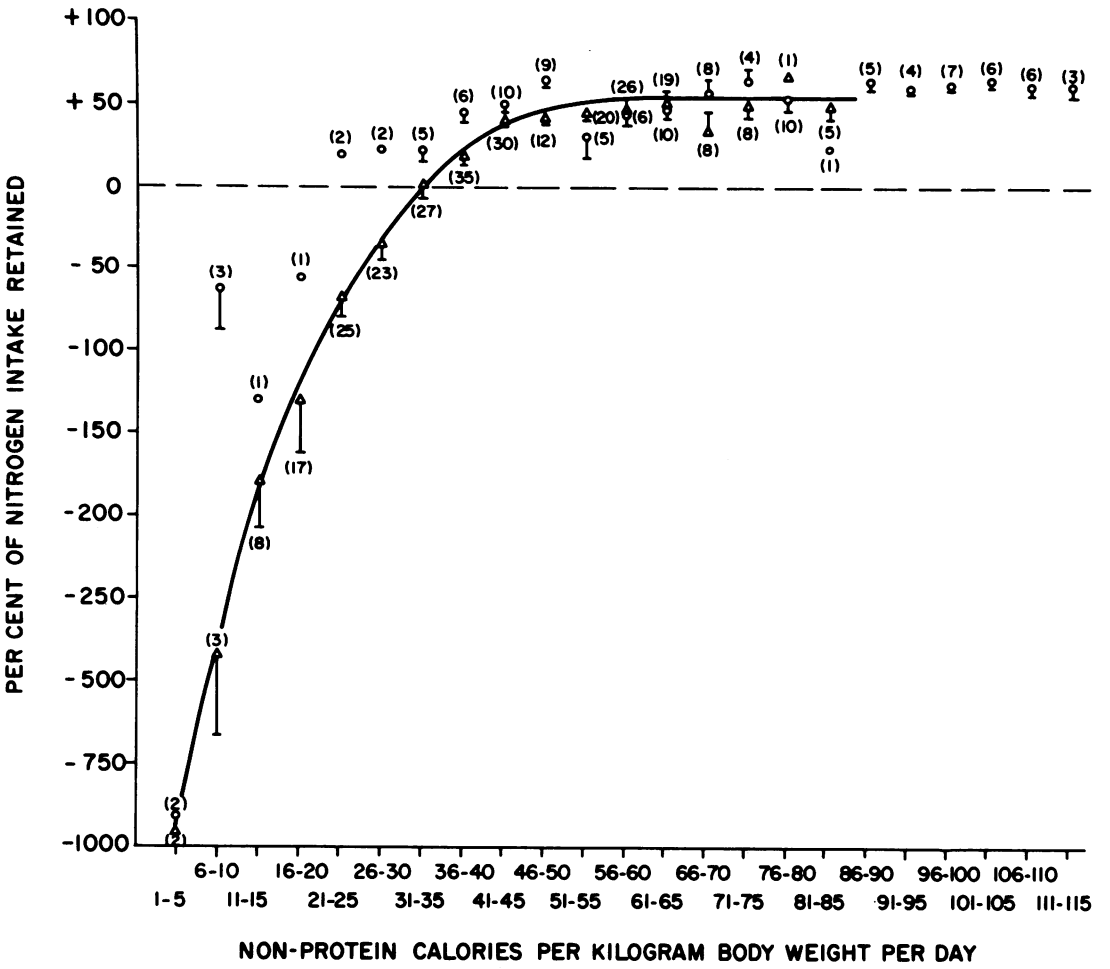


FIG 1. Effect of increasing the daily nonprotein caloric intake on the per cent of infused amino acid nitrogen retained. [Mean ± SEM (number of patients)] ○ Children, △ Adults.

Table 6 outlines the results of selected hepatic function tests performed during the first 20 days of intravenous nutrition. These studies remained normal in those patients with no history or clinical evidence of liver disease. Those patients who had hepatic dysfunction prior to the initiation of parenteral nutrition showed no significant change in these parameters.

*Nitrogen Balance*

Table 7 shows the daily nitrogen balance during the first 30 days of intravenous nutrition. The 12 infants and children studied developed positive nitrogen balance rapidly and this state was maintained throughout the period of intravenous therapy. The majority of the adult patients did not achieve significant positive nitrogen balance until after 10 days of parenteral nutrition. The mean body weights for those patients in whom chronic weights measurements were possible were 6.0 ± 1.8 kg (n = 25) for the 0–13 year age group and 52.0 ± 2.3 kg (n = 43) for the 13–92 year age group.

Nitrogen balance determinations can be misleading, however, unless the contribution of concomitant caloric and nitrogen intake is considered.[15] To assess the effect of nonprotein calories on nitrogen retention from the new amino acid source, the data were examined as shown in Fig. 1. The per cent of nitrogen intake retained was calculated by the formula:

$$\frac{N_{in} - N_{out}}{N_{in}} \times 100,$$

where $N_{in}$ refers to the grams of amino acid nitrogen infused per day and $N_{out}$ refers to the total urinary nitrogen. Nitrogen balance data from the initial day of parenteral nutrition therapy, during and for three days after surgery, sepsis or other severe stress were excluded. In the adult patients studied, the nonprotein calorie/gram amino acid nitrogen ratio of the parenteral nutrition solution was approximately 200/1. The corresponding ratio in pediatric patients was 174/1. As Fig. 1 demonstrates, the most striking increase in nitrogen retention in adult patients occurs from 0–35 nonprotein calories per kg. Nitrogen equilibrium is reached at approximately 35 calories per kg. A plateau of nitrogen retention at 50% of intake is reached when 46–50 non-

protein calories/kg are provided intravenously. The curve appears to be similar for the 0–13 years age group. Insufficient data for lower caloric intakes preclude confident comparison in that region of the curve.

Examination of blood urea nitrogen values at the different levels of caloric intake seen in Fig. 1 showed no significant change for the adult patients but a very slight increase for the infants and children at higher caloric intakes. This increase in BUN (beginning at 8.7 ± 1.3 mg/dl) was approximately 1 mg/dl per increment of 10 nonprotein calories reaching a plateau at 50–60 cal/kg and a BUN of 15.5 mg/dl.

## Discussion

Since parenteral nutrition appeared as a practical reality in 1968,[25] three major complications of its use have been reported; hyperammonemia,[10,11] hyperchloremic metabolic acidosis,[9] and hypophosphatemia.[22,23] These complications have been ascribed to the amino acid composition of the solutions.

Significantly elevated blood ammonia levels have been reported during prolonged parenteral nutrition using either protein hydrolysates[11] or crystalline amino acid solution.[10] Although excessive free ammonia in the infusate may have accounted for the hyperammonemia from the hydrolysates, this was not thought to be the case with the crystalline preparations which contained relatively little free ammonia. The precise etiology of the elevated blood ammonia levels is not known; but the fact that investigators have been able to reverse this metabolic alteration by infusion of 2–3 mm/kg of arginine-HCl or arginine glutamate suggests a possible deficiency of arginine, ornithine, or citrulline in the crystalline amino acid preparations.[10] That a deficiency of these urea cycle intermediates could be at fault was further substantiated by plasma aminograms which showed virtual absence of arginine in the plasma of patients who had been given the crystalline amino acid solutions.[6] A possible explanation is that the amount of infused arginine is insufficient to replace that lost to protein or creatine synthesis. It can be further postulated that this could lead to a deficiency of arginine in the urea cycle thus interfering with the efficient conversion of ammonia to urea. Indirect support is found in the present study for this hypothesis since significant hyperammonemia was not observed with a solution containing nearly three times the amount of arginine as the source used by Heird et al.[10] Although hyperammonemia was not a problem in this series of patients, the occasional elevations found emphasize the importance of weekly or biweekly monitoring of blood ammonia levels in all patients receiving prolonged parenteral nutrition.

Hyperchloremic acidosis, although infrequently seen with protein hydrolysate infusions, has been reported during administration of a crystalline amino acid solution to infants.[9] Amino acids may exist in cationic or anionic forms depending on the pH of their environment. For example at pH 7.4, arginine, histidine, and lysine are cationic; whereas aspartate and glutamate are anionic. Heird and coworkers[9] felt that the mechanism underlying the acidosis seen with the infusion of crystalline amino acid solutions was due to the presence in the infusate of cationic amino acids in excess of anionic amino acids. Acidosis was postulated to result in two ways. First, when the cationic amino acids are balanced by chloride anions in the infusate, catabolism of these amino acids would result in a large amount of remaining nonmetabolizable anion. Plasma chloride and bicarbonate levels have an inverse relationship due to reciprocal renal tubular reabsorption.[19] Therefore, as the plasma chloride content increased, the plasma bicarbonate concentration would be expected to decrease leading to hyperchloremic acidosis.

Secondly, these solutions had a deficit of anionic amino acids. The amount of anionic amino acids required for nascent protein synthesis would be supposedly supplied via transamination from oxaloacetate or $\alpha$-ketoglutarate. The in vivo conversion of glucose into these $\alpha$-keto acids was thought to result in hydrogen ion formation. Heird et al. postulated this hydrogen ion formation contributed to the acidosis.[9] Direct evidence for these mechanisms and the relative contribution of each to the development of metabolic acidosis is unknown at present.

Table 8 compares the amino acid and electrolyte content of the solutions used by Heird et al. with the infant solution used in this study. As can be seen, the anionic amino acids aspartate and glutamate are missing from all three crystalline amino acid solutions. It is also evident that the cationic amino acid and chloride ion concentrations of the solution infused in this study were similar to those used by Heird. Although no definite conclusions can be established regarding the cause for the absence of acidosis in this series, the presumptive cause is the inclusion of more sodium and potassium cations with the presence of a large amount of acetate anion. The rationale for this conclusion is that the acidosis seen by Heird et al. was due to the infusion of nonmetabolizable anion unbalanced by sufficient nonmetabolizable cation.[13] In support of this hypothesis, Kaminski has shown correction and prevention of hyperchloremic acidosis during parenteral nutrition therapy by adding sodium or potassium as the acetate to commercial amino acid infusates.[12]

Heird et al. state that the metabolism of acetate consumes hydrogen ion.[9] Presumably this is a reference to role of acetate in de novo fatty acid biosynthesis, since oxidation of acetate to $CO_2$ via the tricarboxylic acid

TABLE 8. *Crystalline Amino Acid Source Comparison: Amino Acids (m moles/l)*

| | Freamine* | Neoaminosol† | Travasol‡ |
|---|---|---|---|
| Threonine | | | 9.1 |
| Serine | 12.7 | | |
| Aspartate | | | |
| Asparagine | | | |
| Glutamate | | | |
| Glutamine | | | |
| Proline | 19.1 | | 9.4 |
| Glycine | 55.3 | 27.1 | 59.8 |
| Alanine | 15.5 | | 59.8 |
| Valine | 11.1 | 13.6 | 10.1 |
| Cysteine | 0.2 | | |
| Methionine | | | 10.0 |
| Isoleucine | 10.4 | 16.3 | 9.4 |
| Leucine | 13.6 | 47.5 | 12.1 |
| Tyrosine | | | 0.6 |
| Phenylalanine | 6.7 | 6.0 | |
| Tryptophan | 1.5 | 2.4 | 2.3 |
| Lysine | 9.7 | 21.5 | 10.2 |
| Histidine | 4.6 | 7.3 | 7.3 |
| Arginine | 4.1 | 16.3 | 15.3 |
| Electrolytes (meq/L) | | | |
| Sodium | 23.5 | 23.5 | 32.6 |
| Potassium | 15.7 | 15.7 | 30.0 |
| Magnesium | 15.8 | 15.8 | 10.0 |
| Chloride | 23.5 | 23.5 | 32.6 |
| Phosphorus (mg) | 334.0 | 334.0 | 426.0 |
| Calcium | 15.8 | 15.8 | 10.0 |
| Acetate | 10.0 | 0 | 62.7 |
| Total Chloride | 33.3 | 45.0 | 42.8 |

* McGaw Laboratories, Glendale, California.
† Abbott Laboratories, North Chicago, Illinois.
‡ Travenol Laboratories, Morton Grove, Illinois.
Values for Freamine and Neoaminosol solutions calculated from reference 9, Table 1 by using 127.5 ml/kg/24 hr as the mean rate of infusion.

cycle should result in no net change in intracellular hydrogen ion concentration. Another effect of acetate not mentioned by these workers could be the reciprocal renal tubular absorption between organic acid anions and chloride ions.[19] As a result the infusion of acetate could presumably decrease renal reabsorption of chloride ion thus combating the development of hyperchloremic acidosis.

Further controlled experimentation is necessary to delineate the mechanism for the hyperchloremic acidosis found during parenteral nutrition with crystalline amino acids as well as the role of included sodium, potassium and acetate ions in preventing this complication.

Travis et al.[23] and Silvis and Paragas,[22] demonstrated conclusive evidence that hypophosphatemia poses a significant danger during parenteral nutrition. They described a disease state characterized by paresthesias, dysarthria, mental confusion, hyperventilation and lethargy. The red cells in these patients were found to be depleted of 2,3-diphosphoglycerate and ATP causing them to have a greater affinity for oxygen. An inadequate supply of phosphorus in the parenteral nutrition solution is thought to be the cause of this syndrome.[23] Slightly over 400 mg of elemental phosphorus per liter appeared to be adequate to prevent hypophosphatemia in the current study.

The initial slight hypoalbuminemia was not unexpected considering the types of patients included in this study. It was not anticipated, however, that this low serum albumin level would persist once sufficient nutrients were supplied. These data reflect either continued excessive albumin losses, excessive albumin catabolism or impaired albumin synthesis. The effect of acute stress, injury, fever and cancer is to depress albumin synthesis.[21] Also, patients with severe burns[3] and inflammatory bowel disease[24] are known to have persistent large daily albumin losses. When it is considered that many of the adult patients fit into one of the above groups (Table 1) the sustained hypoalbuminemia is more easily understood.

The protein sparing effect of nonprotein calories was demonstrable with the new amino acid source (Fig. 1). Although these data agree closely with the findings of studies related to oral feedings,[2,15] the present study was done in a retrospective manner and a careful prospective demonstration of this effect will be required.

The mean body weight in the adult patients was 52.0 kg. Once positive nitrogen balance was achieved, the mean nitrogen retention was 0.047 gm/kg day. Therefore, on the average, 2.4 gm of nitrogen was retained daily. This should be equivalent to 15.0 gm of protein. Assuming that muscle is approximately 73% water, a 56 gm gain in lean body mass would be expected per day.[14] The mean weight gain for adult patients was 182 gm/day. Therefore, on the average, 31% of the daily weight gain in the patients studied could be explained as a gain of lean body mass. The remainder presumably would represent water and adipose tissue. Since no further direct measurements of lean body mass were studied, these calculations are approximate. Anderson et al.[1] have shown quantitatively similar nitrogen retention in 6 patients with gastrointestinal diesease fed intravenously with the same amino acid source used in this study.

The new amino acid source produced positive nitrogen balance and appropriate weight gain while avoiding previously reported metabolic complications; however, further improvement appears in order. It is likely that the calcium and phosphorus content of the infant solutions should be adjusted closer to that suggested by Ricour et al., thus promoting optimal calcium and phosphorus metabolism for growth.[20] Also, the increase in blood urea nitrogen with the time seen in the infants in this

study suggests that a higher nonprotein calorie/gram nitrogen ratio (174/1 in infant solutions) might be required. This view is supported by Chen et al.,[4] who demonstrated that infusion of a synthetic amino acid solution containing 76% essential amino acids caused an increase in blood urea nitrogen as the calorie/gm nitrogen ratio of the solutions infused into children was decreased from 450/l. At a calorie/gm nitrogen ratio of 175/l, their patients had urea nitrogen levels of 15 mg/dl, similar to the plateau found in the children in the present study when the caloric intake was above 60 cal/kg.

The electrolyte content of the amino acid source necessitated analysis to demonstrate that accumulation of these compounds did not occur (Tables 4 and 5). The inclusion of electrolytes, although providing a safety factor and ease in compounding of the solutions, limits the use of these solutions to patients with relatively normal renal function.

## Acknowledgment

Grateful acknowledgment is given to Mrs. Jane Norman, R.N., for her assistance in data gathering and nursing care supervision of these patients.

## References

1. Anderson, G. H., Patel, D. G., and Jeejeebhoy, K. N. : Design and Evaluation by Nitrogen Balance and Blood Aminograms of an Amino Acid Mixture for Total Parenteral Nutrition of Adults with Gastrointestinal Disease. J. Clin. Invest., 53:904, 1974.
2. Beattie, J., Herbert, P. H., and Bell, D. L.: Nitrogen Balances During Recovery From Severe Undernutrition. Br. J. Nutr., 1:202, 1947.
3. Birtze, J., Liljedahl, S. O., and Plantin, L. O.: Studies on Burns. IX. The Distribution and Losses Through the Wound of $^{131}$I-albumin Measured by the Whole Body Counting. Acta Chir. Scand., 134:27, 1967.
4. Chen, W. J., Ohashi, E., and Kasai, M.: Amino Acid Metabolism in Parenteral Nutrition: With Special Reference to the Calorie: Nitrogen Ratio and Blood Urea Nitrogen Level. Metabolism, 23:1117, 1974.
5. Conway, E. J.: *Microdiffusion Analysis and Volumetric Error.* 3rd Ed. New York, D. Van Nostrand Co., Inc., 1950.
6. Dudrick, S. J., MacFadyen, B. V., Van Buren, C. T., and et al.: Parenteral Hyperalimentation—Metabolic Problems and Solutions. Ann. Surg., 176:259, 1972.
7. Ferrari, A. and Catanzaro, N.: Nitrogen Analysis by a Continuous Digestion System. Ann. N.Y. Acad. Sci., 130:602, 1965.
8. Harper, H. A.: Review of Physiological Chemistry. 13th Ed., Los Altos, Lange Medical Publications, 1971.
9. Heird, W. C., Dell, R. B., Driscoll, J. M., et al: Metabolic Acidosis Resulting from Intravenous Alimentation Mixtures Containing Synthetic Amino Acids. N. Engl. J. Med., 287:19: 943, 1972.
10. Heird, W. C., Nicholson, J. F., Driscoll, J. M., et al.: Hyperammonemia Resulting from Intravenous Alimentation Using a Mixture of Synthetic L-Amino Acids. J. Pediat., 81:162, 1972.
11. Johnson, J. D., Albritton, W. L., and Sunshine, P.: Hyperammonemia Accompanying Parenteral Nutrition in Newborn Infants. J. Pediat., 81:1:154, 1972.
12. Kaminski, M. V.: N. Engl. J. Med. 288:421, 1973.
13. Metabolic Acidosis in Infants Infused with Commercial Amino Acid Mixtures. Nutr. Rev., 31:173, 1973.
14. Moore, F. D.: Metabolic Care of the Surgical Patient. Philadelphia and London, W. B. Saunders Company, 1959; p. 6.
15. Munro, H. N.: Carbohydrate and Fat as Factors in Protein Utilization and Metabolism. Physiol. Rev., 31:449, 1951.
16. Munro, H. N.: *In* Symposium on Total Parenteral Nutrition. AMA Publication, January, 1972.
17. Nelson, W. E.: Textbook of Pediatrics. 8th Ed., Philadelphia and London, W. B. Saunders Co., 1964.
18. Patel, D., Anderson, G. H., and Jeejeebhoy, K. N.: Amino Acid Adequacy of Parenteral Casein Hydrolysate and Oral Cottage Cheese in Patients With Gastrointestinal Disease as Measured by Nitrogen Balance and Blood Aminogram. Gastroenterology, 65:427, 1973.
19. Pitts, R. F.: Physiology of the Kidney and Body Fluids. 2nd Ed., Chicago, Year Book Medical Publishers, Inc., 1972; p. 188.
20. Ricour, C., Millot, M., and Balsan, S.: Phosphorus Depletion in Children on Long Term Total Parenteral Nutrition. Acta. Paediat. Scand., 64:385, 1975.
21. Rothschild, M. A., Oratz, M., and Schreiber, S. S.: Albumin Synthesis. N. Engl. J. Med., 286:816, 1972.
22. Silvis, S. E. and Paragas, P. D., Jr.: Paraesthesias, Weakness, Seizures, and Hypophosphatemia in Patients Receiving Hyperalimentation. Gastroenterology, 62:513, 1972.
23. Travis, S. F., Surgerman, H. J., Ruberg, R. L., et al.: Alterations of Red-Cell Glycolytic Intermediates and Oxygen Transport as a Consequence of Hypophosphatemia in Patients Receiving Intravenous Hyperalimentation. N. Engl. J. Med., 285:763, 1971.
24. Waldmann, T. A., and Strober, W.: Metabolism of Immunoglobulins. Prog. Allergy, 13:1, 1969.
25. Wilmore, D. W. and Dudrick, S. J.: Growth and Development of an Infant Receiving All Nutrients Exclusively by Vein. JAMA, 203:860,1968.