The Effect of Stress Level, Amino Acid Formula, and Nitrogen Dose on Nitrogen Retention in Traumatic and Septic Stress

FRANK CERRA, M.D.* JOHN HIRSCH, M.D.‡ KEVIN MULLEN, M.D.§
GEORGE BLACKBURN, M.D., PH.D.† WAYNE LUTHER, M.D.¶

Eighty-seven patients were entered into a randomized, prospective, double-blind, six-center study to evaluate the effect of amino acid loading and a formula that was branched chain enriched (50%) on nitrogen retention in metabolic stress. The patients had varying levels of metabolic stress (0–3) after major surgery, polytrauma, or surgical sepsis. The study was isocaloric and isonitrogenous and lasted for 7 days. The patients received either a standard amino acid formula (SAA) (Travasol®) or a 50% branched chain enriched formula that was equimolar, leucine, isoleucine, and valine (MAA) (Travasol + Branchamin® concentrate) at a dose of 1.0–2.0 g/kg/day in a fixed ratio with 114 glucose calories per gram of nitrogen administered. The nitrogen retention was proportionate to the nitrogen (and, therefore, caloric) load in both groups. The MAA group, however, had better nitrogen retention, reached nitrogen equilibrium at a lower dose of amino acids, and had less urinary nitrogen excretion per gram of nitrogen administered. Since the groups were isonitrogenous and the calorie to nitrogen ratios were fixed, it appears that nitrogen equilibrium in surgical stress is proportionate to the amino acid load over a range of 0.05–0.4 g/kg/day of nitrogen; and that MAA are more efficient at inducing nitrogen retention and a reduction in urea excretion. These effects on nitrogen retention were more significant at level 2 stress or greater. At these higher stress levels, a dose of 2 ± 0.2 g/kg/day of MAA seemed most efficient in promoting nitrogen retention.

From the University of Minnesota, Minneapolis, Minnesota, SUNY, Buffalo, New York, Harvard University, Cambridge, Massachusetts, Case Western Reserve, Cleveland, Ohio, Washington University, St. Louis, Missouri, and the University of Tennessee

THE METABOLIC RESPONSE to surgery, trauma, and sepsis is in part characterized by reduced total body protein synthesis, increased protein catabolism, increased hepatic protein synthesis, and increased use of amino acids as oxidative fuels.[1–6] The unsupported nitrogen equilibrium is negative, with the degree of negative nitrogen balance proportionate to the degree of metabolic stress.[2,3,7–10,11–13] Exogenous amino acids can reduce this negative balance and can achieve nitrogen equilibrium. This seems to primarily occur by an increase in total body protein synthesis rather than by a reduction in protein catabolism.[8,9,12–15] Whether this is an effect of calories or amino acids, however, has been difficult to assess.

A number of studies have suggested that there are differential requirements for amino acids between organs and differential utilization of amino acids within a given organ.[3,6,12,16] For example, skeletal muscle under conditions of metabolic stress seems to have an increased demand for branched chain amino acids and seems to primarily use them as carbon sources of oxidative energy production; liver demonstrates a reduced capacity to clear the aromatic amino acids and extracts the branched chain amino acids in accord with the need for protein synthesis. Amino acid formulas designed to meet these needs have been shown in some clinical studies to improve nitrogen retention relative to standard formulas; the effect seemed proportionate to the dose.[13,17–19]

Given these observations, a double-blind, randomized, prospective, multicenter clinical study was undertaken in surgical stress to try and determine: (1) whether a modified amino acid formula improves nitrogen retention under conditions of surgical stress; (2) if this nitrogen retention is proportionate to the amino acid load and independent of the caloric load; and (3) if the degree of metabolic stress effects the response to the modified amino acids.

Materials and Methods

The model chosen was a double-blind, randomized, prospective, multicenter clinical trial in patients imme-

* University of Minnesota, SUNY at Buffalo.
† Harvard University.
‡ Washington University, St. Louis, MO.
§ Case Western Reserve.
¶ University of Tennessee.
Reprint requests and correspondence: Frank B. Cerra, M.D., Department of Surgery, University of Minnesota, Box 42, University Hospitals, Minneapolis, MN 55455.
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diately after surgical stress who required intravenous nutritional support as part of their treatment regimen. A fixed calorie-to-nitrogen formula was used with glucose as the calorie source; no fat was given during the 7-day study. The nitrogen load was targeted at 1.0–2.0 g/kg/day and given as either a standard amino acid (SAA) formula (Travasol®) or as a modified amino acid (MAA) formula (Travasol + Branchamin®) with a randomization scheme designed to enter two MAA patients for each SAA patient. If there was to be a difference in nitrogen retention between the two formulas, it should be an expression of the formula type, as the calorie/nitrogen ratio was fixed; *i.e.*, although more calories will be given as the nitrogen load increases, it will occur in a fixed ratio so that differences between the two amino acid formulas should reflect an amino acid effect. All patients were entered by written informed consent after the protocol was approved by the human investigation committee of each participating institution.

Six surgical intensive care units at six University Centers participated in the study (Table 1). The entrance criteria were: surgical patients within 24 hours of major general surgery, polytrauma, or sepsis requiring surgical intervention; entered within 24 hours of resusitation; well nourished or minimally malnourished by clinical exam, albumin 2.5–3.5 g/dL and an absolute lymphocyte count over 1000/μL; in whom nutrition support was part of the therapeutic plan for at least 7 days; and serum creatinine clearance within normal range or creatinine clearance over 20–25 mL/min. Exclusion criteria included: not meeting the entrance criteria; known cirrhosis, pancreatitis, or insulin-dependent diabetes; and the presence of steroids, insulin, chemotherapy, or radiation therapy.

The patients were randomized in a double-blind fashion to receive either a balanced SAA formula (Travasol, 18% branched chain) or the MAA formula. The MAA formula consisted of Travasol to which Branchamin was added. Branchamin is a branched chain concentrate consisting of equimolar amounts of leucine, isoleucine, and valine. When combined, the solution is 50% branched chain. Table 2 summarizes the two formulas. Glucose was used as the carbohydrate source in a fixed ratio of 114 glucose calories/g nitrogen. Thus, each liter of solution (SAA or MAA) consisted of 17.5% glucose in 5.1% amino acids. For each solution, 6 g of amino acid provided 1 g of amino acid nitrogen. Vitamins, minerals, and trace elements were given daily; salts were added as needed to maintain electrolyte balance. No fat source was given during the 7-day study. Other fluids (nonglucose) were given as needed; other therapy (including blood products) was provided as clinically indicated.

The following studies were done on Day 0 before starting nutrition and then on Days 3–4 and Days 6–7 of nutrition therapy: 24-hour urine collection for total urea and total nitrogen and creatinine excretion; complete blood count, protime, serum glutamyl oxaloacetic transaminase, alkaline phosphatase, total bilirubin, blood urea nitrogen, creatinine, calcium, phosphorous, partial thromboplastin time, platelet count, albumin, glucose, and plasma amino acids (venous or arterial).

TABLE 1. *Patient Entry by Study Site*

Site	Control*	MAA†
University of Minnesota, St. Paul Ramsey Medical Center	9	7
State University of New York at Buffalo	7	15
University of Tennessee	2	4
Harvard University, New England Deaconess Hospital	6	12
George Washington University	3	8
Case Western Reserve	7	7
Total	34	53

* Control = Travasol amino acids.
† MAA = Travasol + Branchamin.

The data were analyzed by analysis of variance using standard t-test with $p < 0.05$ as the significance threshold. When comparing regression lines, the Z-score was used as the indicator of significance.

Results

Group Analysis

The study sites and the number of patients entered are summarized in Table 1. No one center skewed the data. The types of patients are listed in Table 3. There were no significant differences between the treatment groups. The

TABLE 2. *Solution Composition*

	Travasol 5.1% (mg/100 mL)	Branchamin 5.1%* (with Travasol) (mg/100 mL)
Essentials		
Isoleucine	306	743
Leucine	372	789
Lysine	296	203
Methionine	204	140
Phenylalanine	286	196
Threonine	214	147
Tryptophan	92	63
Valine	296	736
Nonessentials		
Alanine	1056	725
Arginine	587	403
Histidine	245	168
Proline	347	238
Serine	255	175
Tyrosine	20	14
Glycine	525	361
Cystine	—	—
Asparagine	—	—
Glutamic acid	—	—

* Branchamin 5.1% (with Travasol) + Branchamin 4% (400 mL) + Travasol 10% (350 mL)

TABLE 3. *Case Distribution*

Type	%	Type
Elective surgery total	35	Gastrectomy, esophagectomy
Control	42	Pseudocyst, major vascular
MAA	58	Common duct exploration, small bowel resection
Trauma	17	Major polytrauma, burns
Control	22	
MAA	78	
Sepsis	48	Diverticulitis, bowel infarction
Control	42	Colon perforation, penetrating
MAA	58	Trauma, pneumonia, cholangitis
Sex		
Control		
Male	50	
Female	50	
MAA		
Male	75	
Female	25	
Age (years)		
Control	50 ± 14	
MAA	59 ± 15	

entrance data are summarized in Tables 4 and 5. The patients were well nourished or minimally malnourished.

There were no differences in the amount of calories or nitrogen administered between SAA or MAA on any study day. Renal function was stable throughout the 7-day study. The urine creatinine excretion was consistent with reasonable urine collection technique. The nitrogen balance is presented in Figure 1. The nitrogen retention achieved significance by Days 3–4 of the study in MAA and remained as such on Days 6–7.

Although there were no differences in the amount of nitrogen given on any study day between SAA and MAA, there was some variance in the amount of nitrogen given on any given day in both MAA and SAA. This variance was not different between MAA and SAA and ranged from 0.05–0.40 g/kg/day of nitrogen. As the study was designed to evaluate the effect of nutrition input (SAA or MAA), Figure 1 was then recalculated using those patients who received over 0.1 g/kg/day of nitrogen; the same significance was obtained with an increased level of nitrogen retention. In an effort to further evaluate the relationship between nitrogen retained and nitrogen given and because of the variance in dosing, the nitrogen given was converted to g/kg/day and replotted. Figure 2 presents nitrogen balance as a function of the dose of amino acids given. There is a significant increase in nitrogen accrual in MAA. Nitrogen equilibrium is achieved at 0.2 g/kg/day of nitrogen in SAA and 0.14 g/kg/day of nitrogen in MAA.

When the nitrogen excretion is approached in the same manner, the MAA group demonstrates less total nitrogen excretion per gram of nitrogen administered than does the SAA group (Fig. 3). When a cost analysis was done using current costs for products at the University of Minnesota, it was $2.03 per gram of SAA given and $1.63 per gram of MAA given to achieve nitrogen equilibrium.

The plasma amino acids demonstrated elevations of the branched chain amino acids in MAA. The alkaline phosphatase and total bilirubin tended to rise in both SAA and MAA. The trend was for less rise in MAA, but it did not reach statistical significance between SAA and MAA.

Stress Level Analysis

Stress level was judged by the amount of nitrogen excretion in the urine in the 24-hour urine collection done before initiating nutritional support and within 24 hours of injury. Level 0 had 0–5 g total nitrogen/day; level 1, 5–10; level 2, 10–15; and level 3, over 15 g/day.[13] The percent distribution is presented in Table 6. The correlation between the clinical setting of stress (postoperative general surgery, polytrauma, sepsis) and the amount of

TABLE 4. *Chemistry Summary**

	SAA			MAA		
	Day: Base	Mid	End	Day: Base	Mid	End
Albumin (g/dL)	3.1 ± 0.7	2.9 ± 0.7	3.1 ± 0.6	2.8 ± 0.6	2.8 ± 0.6	2.9 ± 0.7
Total protein (g/dL)	5.3 ± 1.3	5.7 ± 0.7	5.9 ± 0.6	4.9 ± 0.7	5.3 ± 0.9	5.9 ± 1.0
Glucose (mg/dL)	158 ± 56	194 ± 72	171 ± 60	161 ± 81	199 ± 85	148 ± 69
Total bilirubin (mg/dL)	1.9 ± 2.2	1.4 ± 1.5	2.9 ± 3.0	1.9 ± 1.7	1.8 ± 2.1	2.2 ± 2.8
AST (U)	106 ± 68	150 ± 107	182 ± 121	102 ± 68	127 ± 59	179 ± 83
SGOT (U)	79 ± 104	48 ± 39	65 ± 53	71 ± 104	58 ± 53	57 ± 32
LDH (U)	350 ± 172	313 ± 152	336 ± 141	378 ± 209	353 ± 124	339 ± 137
Alk Phos (U)	106 ± 68	150 ± 107	182 ± 121	102 ± 68	127 ± 59	179 ± 83
Protime (sec)	12.1 ± 3.0	9.5 ± 4.4	9.9 ± 4.7	11.6 ± 4.3	7.6 ± 6.0	7.4 ± 6.0
PTT (sec)	35.7 ± 17.2	27 ± 15.5	29.9 ± 23	30 ± 12	21.8 ± 17.8	19.3 ± 16.3
Platelets ($\times 10^3/\mu L$)	206 ± 156	226 ± 152	225 ± 165	169 ± 148	175 ± 169	200 ± 209
Hemoglobin (g/dL)	11.3 ± 2.5	11.9 ± 1.5	11.3 ± 1.1	10.6 ± 3.4	11.3 ± 0.7	11.5 ± 1.1
White count ($\times 10^3/\mu L$)	13.4 ± 7.9	13.1 ± 5.6	13.8 ± 6.6	12.6 ± 13	18.1 ± 20.1	24.8 ± 35.6
% Lymphocytes (%)	12.3 ± 8.2	12.2 ± 6.3	14.6 ± 4.6	12.8 ± 12.7	11.3 ± 7.2	11.1 ± 7.5

* Mean ± SD.

TABLE 5. *Nitrogen Summary**

	SAA			MAA		
	Day: Base	Mid	End	Day: Base	Mid	End
In						
Nitrogen (g/day)	1.7 ± 3.8	7.1 ± 6.1	8.4 ± 5.5	1.1 ± 2.3	8.6 ± 5.1	9.1 ± 5.2
Nitrogen (g/kg/day)	0.05 ± 0.07	0.07 ± 0.06	0.14 ± 0.09	0.01 ± 0.03	0.15 ± 0.06	0.16 ± 0.13
Urine						
Urea (g/day)	8.3 ± 3.2	9.4 ± 4.6	7.9 ± 4.2	10.2 ± 11.8	9.4 ± 4.5	7.9 ± 4.0
Total N (g/day)	8.8 ± 4.6	9.5 ± 5.3	9.8 ± 4.3	10.3 ± 7.8	9.5 ± 3.5	9.8 ± 5.3
Creatinine (g/day)	1.2 ± 0.6	0.97 ± 0.5	0.8 ± 0.4	1.0 ± 0.5	1.1 ± 0.5	1.0 ± 0.5
Balance (g/day)	−7.8 ± 4.9	−1.7 ± 4.9	−1.5 ± 5.7	−9.6 ± 7.2	1.4 ± 5.4†	1.8 ± 4.8†
Blood						
BUN (mg/dL)	22 ± 13	17 ± 10	24 ± 20	19 ± 15	23 ± 18	27 ± 32
Creatinine (mg/dL)	1.4 ± 1.1	1.0 ± 0.3	1.5 ± 1.4	1.2 ± 0.6	0.9 ± 1.2	1.4 ± 2.7
Plasma						
Glutamine (μM/L)	269 ± 180	161 ± 193	121 ± 168	235 ± 189	163 ± 184	205 ± 189
Leucine (μM/L)	80 ± 34	55 ± 49	73 ± 68	93 ± 51	110 ± 91†	140 ± 130†
Isoleucine (μM/L)	39 ± 24	37 ± 36	49 ± 48	45 ± 32	85 ± 75	113 ± 122†
Valine (μM/L)	175 ± 65	136 ± 121	167 ± 148	191 ± 117	286 ± 284†	340 ± 277†
Phenylalanine (μM/L)	76 ± 38	63 ± 59	70 ± 67	77 ± 65	58 ± 51	67 ± 50
Tyrosine (μM/L)	46 ± 22	24 ± 24	34 ± 28	47 ± 23	23 ± 22	33 ± 27
Methionine (μM/L)	20 ± 10	20 ± 18	27 ± 25	19 ± 11	15 ± 14	23 ± 17

* Mean ± SD. † $p < 0.05$.

metabolic stress present as judged from the Day 0 urinary nitrogen excretion had r = 0.5.

Analysis of variance was then performed at each stress level; the data is summarized in Table 7. In level 0 and 1 stress, there was no significant difference in the rate of nitrogen retention between MAA and SAA. There was greater retention per gram of nitrogen administered in level 2 and 3 stress with the MAA.

Since the theory would predict that the nitrogen retention effect should be proportionate to the degree of metabolic stress, the slope of the SAA and MAA groups at each stress level was analyzed and is shown in Figure 4.

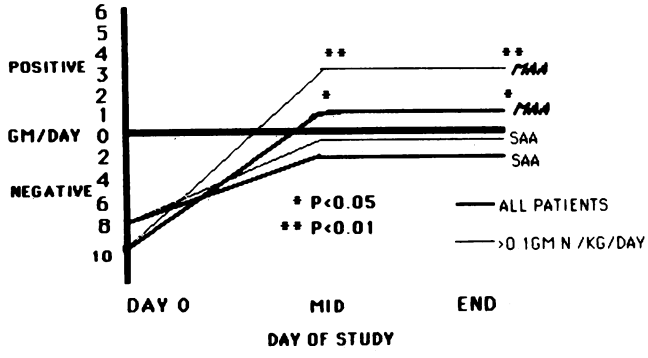

FIG. 1. The nitrogen balance before study initiation and then at midstudy (days 3–4) and at the end of the study (days 6–7). The dark, wide line represents all patients in either the control (SAA) or MAA group. As some patients did not reach their target dose, only those patients receiving at least 0.1 g/kg/day of nitrogen are plotted in the lighter, thinner line. In either case, there was better nitrogen retention in the MAA group.

The nitrogen retention effect of SAA and MAA loading is proportionate to the amount of metabolic response present, with a major effect at level 2 or greater.

Discussion

In the presence of significant metabolic stress and the absence of the organ failure syndrome, the influence of the type of amino acid formula administered on nitrogen retention was assessed using a 7-day randomized, double-

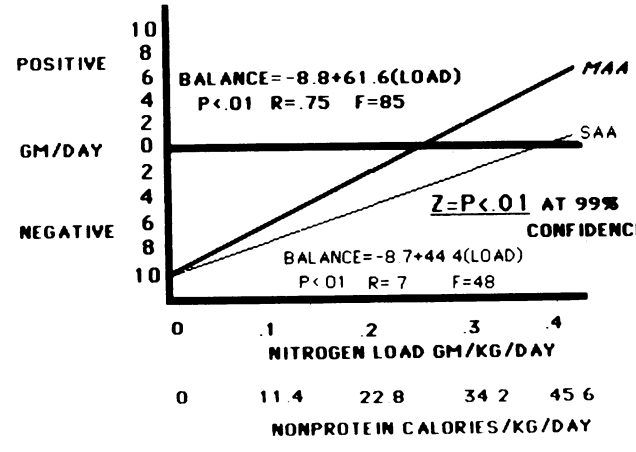

FIG. 2. Nitrogen balance *versus* nitrogen load. Nitrogen balance (retention) is affected by the nitrogen load administered. The Z statistic indicates that there is greater nitrogen retention per g nitrogen/kg input with the MAA. The nonprotein calorie to nitrogen ratio is constant in both groups throughout the study; this difference in nitrogen retention effect must reflect an effect of the amino acid formula.

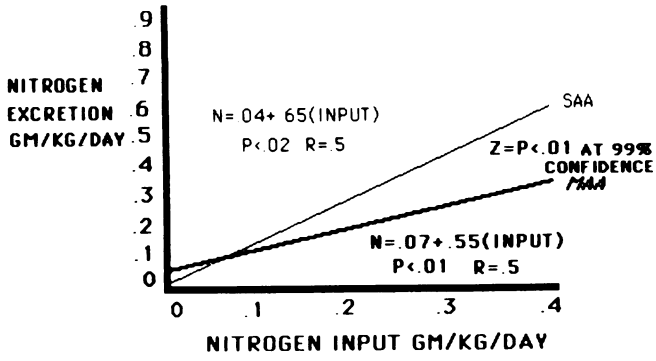

FIG. 3. Nitrogen excretion *versus* nitrogen input. The study was isonitrogenous. Since there was greater nitrogen retention in MAA, the expectation would be for less nitrogen excretion per g nitrogen input/kg. This was the effect observed. 85 ± 5% of the total nitrogen excreted was as urea. The implication is one of a relative reduction in ureagenesis during MAA infusion.

TABLE 7. *Relationship of Nitrogen Balance to Stress Level and Nitrogen Dose Given*

Stress Level	Intercept	β-Coefficient	Coefficient of Determination	p-Value for Regression
0				
Control	−6.8	43.3	0.14	0.13
MAA	−3.0	36.6	0.64	0.01
1				
Control	−7.6	35.1	0.59	<0.001
MAA	−5.9	44.5	0.47	<0.001
2				
Control	−12.7	65.2	0.91	<0.001
MAA	−13.2	88.9*	0.68	<0.001
3				
Control	−12.2	56.5	0.74	0.06
MAA	−22.5	165*	0.77	<0.001

* $p \leq 0.05$ MAA *versus* control.

blind, prospective, multicenter study design. Improved nitrogen retention was observed in the MAA group. As the calorie/nitrogen ratio was fixed, the improved nitrogen retention was probably an influence of the amino acid formula. The effect was also dose dependent, with nitrogen equilibrium reached at a lower level of MAA administration than SAA. The effect was also dependent on the amount of existing metabolic stress with the major effect at level 2 or greater.

The variance in amino acid dosing is a clinical problem and is probably present in many studies. Given the dose-dependency observed in the nitrogen retention, the dosing variance may help to explain why MAA support has not been found to be uniformly beneficial in surgical stress. More recent studies, however, have also observed improved nitrogen retention with MAA.[17-19] The dose-dependency would also seem to imply a drug effect.[17] Perhaps the concepts of pharmacokinetics and pharmacodynamics would be well applied to metabolic studies.

The dose-dependency of nitrogen retention has been previously observed.[19] The precise origin of this phenomenon is unclear. Perhaps it is related to the increased catabolism present in surgical stress. Since exogenous amino acids can stimulate total body protein synthesis[3,8,9,11-13] and since the degree of catabolism is dependent on the degree of stress,[1,2,4,14,13] perhaps a larger dose of amino acids is necessary to achieve equivalency with the rate of catabolism. Another observation is that there is an increased use of amino acids as oxidative fuels in surgical stress.[4,7-10] The attainment of nitrogen equilibrium might require this need also being met. Thus, the demand for amino acids seems increased both by the demands for protein synthesis *and* energy production. These needs would require increased dosing to achieve equilibrium.

The level of metabolic stress also influenced the nitrogen retention effect. The theory would indicate greater demand for amino acids, particularly the branched chains, as the level of metabolic stress increases in order to meet the increasing demands for protein synthesis and amino acid-derived energy production. The data demonstrated

TABLE 6. *Patient Distribution by Stress Level*

Urinary Nitrogen on Day 0 (g/day)	Stress Level	%	
		Control	MAA
0–5	0	14	14
5–10	1	55	45
10–15	2	23	21
Over 15	3	8	10

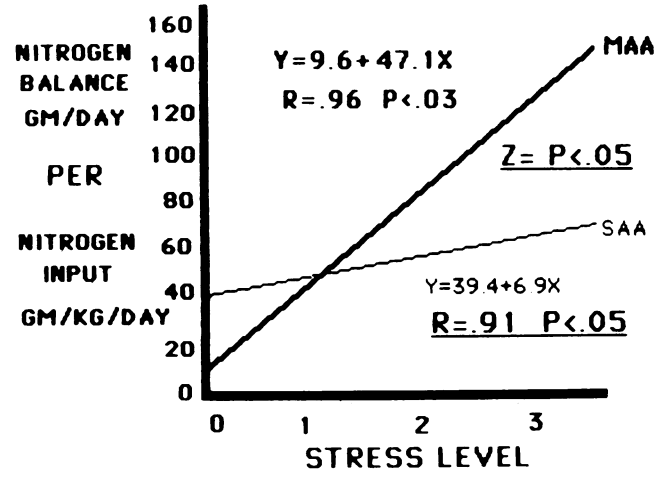

FIG. 4. Effect of stress level on nitrogen retention. The slope of each dose-response curve at each stress level is plotted. The rate of nitrogen accretion is proportionate to the amount of metabolic stress. The major separation between MAA and SAA occurs at level 2 stress or greater. The MAA are more efficient amino acid sources at the higher levels of metabolic stress.

an improved metabolic effect of the MAA at the higher levels of stress when adequate doses of MAA are given.

Thus, two factors seem important in the MAA effect on nitrogen retention: the amount of metabolic stress and the dose administered. All patients were within 24 hours of injury. Of note is the poor correlation between clinical setting and the degree of metabolic stress observed. The optimum dose of amino acids at level 2 stress or greater seems to be 2 ± 0.2 g/kg/day.

No effect was observed on albumin by either MAA or SAA. In part, this may be related to the long turnover of albumin. In the presence of metabolic stress, however, mediators like Interleukin I seem to stimulate hepatic acute phase protein production while decreasing the production of the nutritional sensitive proteins such as albumin.[20,21] In other double-blind, randomized, prospective studies, MAA were shown to stimulate the production of transferrin and retinol-binding protein, at least as assessed by changes in serum concentration.[18,19] This stimulation of the hepatic nutrition-sensitive proteins has also been correlated with improved survivability.[15] Since only albumin was measured and there were no deaths in this acute study of 7 days, these later findings could not be assessed.

It is difficult to distinguish from this study what component of the MAA is responsible for the effect. Previous experimental work would implicate the branched chain amino acids, particularly leucine. As the composition of the nonbranched chain amino acids was also changed, the correlations would also hold for that variable in this study. In a study comparing leucine heavy and valine heavy MAA in surgical stress, however, only the leucine heavy formula had the predominant effect.[19]

Nitrogen retention, then, seems to be a function of the degree of metabolic stress present, the dose of amino acids given, and the type of amino acid formula. The amount of metabolic stress present is poorly predicted from the clinical setting. The MAA effect on nitrogen retention appears to require moderate to high level stress (over level 2) and a dose 2 ± 0.2 g/kg/day for maximum results. In this context, the MAA were also cheaper to give per gram of amino acid necessary to achieve nitrogen equilibrium during metabolic stress.

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