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Treatment of malnourished CAPD patients with an amino acid based dialysate

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Treatment of malnourished CAPD patients with an amino acid based dialysate. Nineteen malnourished chronic peritoneal dialysis patients who were ingesting a low protein intake underwent metabolic balance studies to test whether a dialysate that contained amino acids would improve their protein nutrition. Patients lived in the hospital for 35 days while they ate a constant diet and underwent their usual regimen of continuous ambulatory peritoneal dialysis (CAPD). The first 15 days served as a Baseline Phase. For the last 20 days, the usual dialysate was substituted with a dialysate of essentially the same composition except that it contained 1.1% essential and nonessential amino acids and no glucose. Patients received one or two dialysate exchanges with amino acids each day depending on the amount necessary to bring the individual's dietary protein plus dialysate amino acid intake to 1.1 to 1.3 g/kg body weight/day. During Baseline, patients were in neutral nitrogen balance; net protein anabolism was positive, as determined from ^{15}N-glycine studies. After commencing intraperitoneal amino acid therapy, nitrogen balance became significantly positive, there was a significant increase in net protein anabolism, the fasting morning plasma amino acid pattern became more normal, and serum total protein and transferrin concentrations rose. Patients generally tolerated the treatment well, although some patients developed mild metabolic acidemia. These findings indicate that a dialysate containing amino acids may improve protein malnutrition in CAPD patients ingesting low protein intakes.

Recent studies indicate that many adult patients undergoing either maintenance hemodialysis or chronic peritoneal dialysis show evidence for protein-calorie malnutrition [1–7]. The incidence of malnutrition in chronic peritoneal dialysis patients is reported to range from about 18 to 59% [4–7]. Severe malnutrition is reported to occur in 8 to 37% of patients [4–7]. Although many factors may engender malnutrition in maintenance peritoneal dialysis patients, inadequate intake of protein and calories appears to be an important cause. Protein and amino acid losses in dialysate may intensify protein malnutrition in these patients [8, 9]. Since malnutrition may be an important risk factor for morbidity and mortality in chronic peritoneal dialysis patients [10, 11], this problem is of considerable clinical importance.

Several investigators have examined the nutritional benefits of substituting amino acids for glucose in peritoneal dialysis solutions [12–20]. This treatment should both augment the amino acid intake and reduce the net amino acid losses of the patient, thereby increasing the net intake of protein precursors. In most but not all studies, the treatment with dialysate containing amino acids was associated with improvement in nutritional indicators, including increased serum proteins [12, 15, 18, 19], normalization of the plasma amino acid profile [14, 18], increased nitrogen balance [14, 20], and weight gain [14, 19]. In a number of these studies, malnutrition or low protein intake was not a requirement for patient selection. Moreover, there was little or no attempt to control the dietary nutrient intake of the patients before and during the treatment with intraperitoneal amino acids. If low nutrient intake was not a cause of malnutrition, dialysate with amino acids might not be expected to improve nutritional status. Also, the nitrogen balance data were obtained over very short periods of time and sometimes by estimating total nitrogen intake and output.

The present multicenter study was undertaken to assess the nutritional and metabolic effects of an amino acid dialysis solution in malnourished patients undergoing chronic peritoneal dialysis. Each patient had a documented marginal or low protein intake that was considered to be a cause of their malnutrition. During the study, each patient was hospitalized for 35 days and received a constant protein and energy diet in order to exclude the possibility that a change in dietary intake might influence the metabolic response during the study. After a 15 day Baseline Phase, patients entered a Treatment Phase where one or two exchanges of dialysate containing 1.1% amino acids were substituted for one or two standard dialysates containing D-glucose. The results indicate that treatment with one or two amino acid dialysis solutions each day increased nitrogen balance, protein turnover and net protein accrual, raised serum total protein and transferrin levels, and tended to normalize several postabsorptive plasma amino acid concentrations.

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Methods

Patients

This was a multicenter study involving 24 patients from the Divisions of Nephrology from the following medical centers (parentheses indicate the number of subjects who successfully completed the study at each individual center): Boston University (5), Harbor-UCLA Medical Center (5), University of Michigan (4), Karolinska Institute (3), and University of Iowa (2). Five patients were discontinued from the study for the following reasons: two episodes of peritonitis occurred during the Baseline Phase, and a third occurred on the third day of treatment with amino acid dialysate. One patient was discharged from the study during the Baseline Phase because of generalized debility preventing compliance to the protocol. The fifth patient was discontinued from the study on the third day of the Treatment Phase because of an incarcerated hernia associated with nausea. Data from the remaining 19 patients who completed the study comprise the body of this report.

The major patient eligibility criteria for participation in the study included the following: a diagnosis of protein malnutrition based on the following criteria: (a) evidence for muscle wasting by clinical appraisal or a decrease in mid-arm muscle circumference; (b) a body weight of 90% or less of desirable body weight or a serum albumin of 4.0 g/dl or less in men and 3.7 g/dl or lower in women; and (c) an inadequate dietary protein intake prior to entering the study (that is, a protein intake of 1.0 g/kg actual body weight per day or less). Desirable body weight is determined as the median weight of individuals of the same age range, gender, height and frame size as the patient as determined from the 1983 Metropolitan Life actuarial tables [21]. Dietary intake was determined from a five day dietary diary kept by the patient and a dietary interview with a dietitian during the screening period before the patient was accepted into the study. Other inclusion criteria for the study were treatment with continuous ambulatory peritoneal dialysis (CAPD) or continuous cyclic peritoneal dialysis for at least four months and ages 18 to 75 years. Patients were excluded if their renal creatinine clearance was greater than 5.0 ml/min or if they had insulin dependent diabetes mellitus, any illness requiring hospitalization within 30 days, one episode of peritonitis within the past month, more than one episode of peritonitis in the past six months, the presence of cancer except basal cell carcinoma, severe liver, lung or heart failure, vasculitis, psychosis, or if they were not clinically stable. This study was approved by the institutional review board from each participating clinical center. All patients gave informed written consent before commencing the study.

Upon entering the study, patients lived in a clinical research center for 35 days. An exception were the three subjects studied in Sweden who lived in a general nephrology ward but whose meals were prepared in a kitchen modified for metabolic balance studies. Throughout the 35 day study, patients were fed a constant diet that was calculated to provide 0.80 g protein (allowable range, 0.70 to 0.90)/kg actual body weight/day and an energy intake estimated to meet the patient's energy requirements, 28 ± 3 kcal/kg/day (range, 23 to 38). For each individual patient, the daily intake of both energy and protein was divided into portions of approximately 2/8, 2/8, 3/8 and 1/8 for consumption at breakfast, lunch, supper and the snack. Dietary fat, sodium and potassium intake was designed to be similar to the patient's prestudy intake. The diets were prepared using metabolic kitchen protocols that have been employed in previous studies [22]. Any changes in food intake were strongly discouraged after the first three to four days of the study. All patients were given one tablet per day of a multivitamin supplement. Many patients also received other medicines typically prescribed for chronic dialysis patients including antihypertensive medications, erythropoietin, phosphate binders, and various other agents. No patient was started or stopped on erythropoietin therapy or any other anabolic or catabolic medicines (for example, corticosteroids) during or within several weeks before commencing the study.

The first 15 days of the study were considered a Baseline Phase during which each patient underwent a CAPD regimen similar to his/her prestudy treatment. Eighteen patients received four dialysate exchanges per day and one patient received five exchanges daily. For the four daily exchanges, the instillation of fresh dialysate was generally started at 8:00 a.m. (after the morning blood drawing), 1:00 p.m., 5:00 p.m., and 11:00 p.m. Drainage of dialysate was initiated about 15 minutes before instillation except for the morning drainage which was begun at 7:30 a.m. to allow time for weighing the patient and for blood drawing before the 8:00 a.m. instillation. Dianeal® 1.5%, 2.5% and 4.25%, (Baxter Healthcare, Deerfield, IL, USA) were the dialysate solutions used during the study (anhydrous glucose concentrations; 1.36, 2.27, and 3.86 g/dl, respectively). Electrolyte composition of Dianeal® (in mEq/liter) was sodium 132, calcium 3.5, magnesium 0.5, chloride 96, and lactate 40. Fifteen patients used two liter bags for all exchanges throughout the study; three individuals used 1.5 liter exchanges for Dianeal® and 2.0 liter exchanges for the amino acid dialysate solutions; and one patient used 1.5 liter bags exclusively (including the dialysate with amino acids) during the study.

During the Treatment Phase, from days 16 to 35, patients continued to undergo the same dietary and dialysis regimen except that each day the patients received one or two dialysate exchanges containing 1.1% amino acids and no glucose instead of one or two of the regular 1.5% dextrose dialysate solutions. The number of exchanges with amino acids that patients were given was calculated so as to provide a total daily dietary protein plus dialysate amino acid intake of 1.1 to 1.3 g/kg/day (assuming absorption of about 80% of the instilled amino acids [15]), which is similar to previously recommended protein intakes for CAPD patients [22]. All patients received the dialysate with 1.1% amino acids at the 8:00 a.m. exchange. The second amino acid exchange, which was given to nine patients, was instilled at 5:00 p.m. Thus, both amino acid exchanges were administered when patients were in the postprandial state. Intraperitoneal amino acid treatment was reduced from two to one exchange per day if the serum urea nitrogen (SUN) rose to 112 mg/dl (40 mmol) or greater or if uremic symptoms developed.

The composition of the dialysate with 1.1% amino acids was as follows: amino acids (in mg/dl) histidine 71, isoleucine 85, methionine 85, leucine 102, lysine 76 (added as 95 mg of the hydrochloride salt), phenylalanine 57, threonine 65, tryptophan 27, valine 139, tyrosine 30, alanine 95, arginine 107, glycine 51, proline 59, and serine 51. Electrolyte composition was the same as with the Dianeal® solution except for the chloride concentration which was 105 mEq/liter with the amino acid dialysate. The calculated osmolarity was 365, and the pH was approximately 6.2.

Nitrogen balances were measured continuously in each patient from days 6 through 15 of the Baseline Phase and from days 21

through 35 of the Treatment Phase, using previously described techniques [22]. Total nitrogen was measured in duplicate 24 hour diets, at least five times during the study in each patient, in each 24 hour pool of dialysate outflow, in urine collected daily or, for oliguric patients with less than 500 ml urine output per day, in five day urine pools, and in feces collected during the same five day pools. Nitrogen balances were calculated for each of the five day collection periods and were adjusted for changes in body urea nitrogen as previously described [23].

Blood for measurement of serum urea, creatinine, and albumin was obtained in the postabsorptive state after an overnight fast between 7:45 and 8:00 a.m. at the beginning of days 1, 6, 11, 16, 21, 26, 31 and at the end of day 35 (that is, the beginning of day 36). Serum total protein, transferrin, potassium, phosphorus and HDL, LDL, and VLDL cholesterol were obtained for measurement at the beginning of days 1, 16, and 36. Blood for plasma amino acid analyses was drawn after an overnight fast between 7:45 and 8:00 a.m. at the beginning of days 1, 16, 26 and 36. Arterialized venous blood pH and pCO_2 were determined in seven patients on days 5, 10, 25 and 33.

The blood for amino acid analyses was collected in tubes containing dry heparin and was centrifuged immediately at 2,300 g for 15 minutes at 4°C. One milliliter of the supernatant was pipetted off, taking care not to disturb the buffy coat, and added to 45 mg of crystalline sulfosalicylic acid. After mixing, the preparation was centrifuged for 15 minutes. The supernatant was quickly pipetted into another tube and frozen at −60 to −70°C until analyzed. The amino acid analyses were usually performed within one month of obtaining the plasma. For collection of arterialized venous blood, the blood was obtained from the antecubital vein before the first morning exchange. The arm was first wrapped in hot towels to increase blood flow. Blood was drawn without using a tourniquet using anaerobic techniques.

Starting on days 8 and 26, patients underwent measurements of total body protein turnover as described by Fern et al [24]. The foregoing method was modified in that both pooled 24-hour dialysate outflow and urine (if patients made urine) were collected daily for longer periods, from days 6 to 15 and Days 24 to 33 because of the below normal urea clearances of our patients. For each turnover study, after an overnight fast, patients ingested 5 mg/kg body weight of ^{15}N-glycine 99 atom % (Merck and Co. Inc./Isotopes, Quebec, Canada) before breakfast. The purity of the ^{15}N-glycine content of the isotope ingested was confirmed by mass spectroscopic and total nitrogen analyses. Calculation of protein synthesis, degradation and flux was performed as previously described [24], except that the ^{15}N enrichment in total nitrogen was measured and the results in dialysate and urine were pooled.

Serum albumin and transferrin were measured in samples from all five centers in a central laboratory at SmithKline Bio-Science Laboratories (Van Nuys, CA, USA). Albumin was assayed by the bromcresol green method and transferrin by nephelometry. Plasma amino acids were determined with a Beckman Model 6300 Amino Acid Analyzer using a lithium buffer system in a Central Amino Acid Laboratory (University of Iowa, L. Stegink, Director). Total nitrogen was measured by pyrochemiluminescence with an Antek Nitrogen Analyzer Model 401 (Antek Instruments, Inc., Houston, TX, USA) in the Metabolic Laboratory, Critical Care Diagnostic Service, Department of Surgery, University of Michigan (Ann Arbor, MI, USA, R. Dechert, Director). ^{15}N was measured at the Mass Spectrometry Resource (Washington University, St. Louis, MO, USA) using a Nuclide 3-60 Isotope Ratio Mass Spectrometer. Serum urea nitrogen, creatinine, total protein, lipids, lipoproteins, blood pH and pCO_2, and other chemistries were determined in the hospital laboratory at each participating center.

Table 1. Characteristics of patients

	Total	Male	Female
Number of patients	19	14	5
Age, *years*	54 ± 13[a]	57 ± 11	47 ± 15
Body weight, *kg*	68 ± 12	69 ± 12	63 ± 10
Height, *cm*	171 ± 9	172 ± 10	168 ± 6
Relative body weight, %[b]	91 ± 13	92 ± 13	90 ± 11
Race, ethnic background			
Asian	1	1	0
Afro-American	4	1	3
Caucasian	13	11	2
Hispanic	1	1	0
Duration of CAPD, *years*	2.3 ± 2.3 (0.4–8.8)[c]	2.6 ± 2.5 (0.7–8.8)	1.3 ± 0.7 (0.4–2.3)
Prestudy dietary intake			
Protein, g/kg/day[d]	0.91 ± 0.12	0.88 ± 0.12	0.98 ± 0.08
Energy, kcal/kg/day[d,e]	24.9 ± 5.7	24.3 ± 5.9	26.7 ± 5.4
Creatinine clearance, ml/min	2.0 ± 1.8 (0.0–5.0)	1.9 ± 2.0 (0.0–5.0)	2.2 ± 1.5 (0.0–4.0)

[a] Mean ± standard deviation; [b] (Current body weight/median Metropolitan Life body weight for person of same gender, height, and frame size) × 100%; [c] Parentheses indicate range of values; [d] Calculated from 5 day dietary diaries and interviews; [e] Refers to intake from diet, and not dialysate.

Statistics

Data were analyzed by analysis of variance (ANOVA) and paired *t*-tests. Statistical significance was evaluated by the paired *t*-test if the data were normally distributed and by the signed rank test if the data were not normally distributed. The nitrogen balance data were analyzed by a repeated measures multivariable ANOVA. Since a significant time versus treatment interaction was observed, paired *t*-tests were performed comparing days 6 through 10 to days 21 through 25, days 11 through 15 to days 26 through 30 and also the averages of the two control periods to the three treatment periods. Data are expressed as mean ± standard deviation.

Results

Characteristics of the 19 patients are shown in Tables 1 and 2. As is apparent from their relative body weight, serum proteins and dietary protein and energy intake, both protein and calorie malnutrition were present in many patients. Fourteen patients had a clinical appraisal of muscle wasting; midarm muscle circumference (MAMC) was in the 25th percentile or lower in 14 patients; relative body weight (RBW) was 86% or lower in 11 patients; and the serum albumin concentration was 3.6 g/dl or lower in 16 subjects (range of serum albumin in 19 patients, 2.3 to 3.9 g/dl). Eight patients had a clinical appraisal of muscle wasting, a MAMC in the 25th percentile or lower, a RBW of 86% or lower, and a serum albumin of 3.6 g/dl or lower. Five patients showed three of these four characteristics, five patients displayed two of these characteristics, and one patient showed one characteristic. Renal failure was caused by idiopathic glomerulonephritis in nine

Table 2. Serum chemistries during the course of study

	Onset of Baseline (Day 0)[a]	End of Baseline (Day 16)[b]	End of treatment phase (Day 36)[c]	*P* values	
				Day 16 vs. Day 0	Day 36 vs. Day 16
Urea nitrogen, *mg/dl*	60 ± 16	49 ± 12	77 ± 22	0.0001	0.0001
Urea, *mmol/liter*	21 ± 6	17 ± 4	27 ± 8		
Creatinine, *mg/dl*	11.5 ± 3.4	10.8 ± 3.1	10.8 ± 3.0	0.016	NS
mmol/liter	1017 ± 301	955 ± 274	955 ± 265		
Potassium, *mEq/liter*	4.1 ± 0.4	4.2 ± 0.7	3.9 ± 0.6	NS	0.031
Phosphorus, *mg/dl*	5.6 ± 1.4	4.8 ± 1.4	3.8 ± 1.7	0.017	0.0061
mmol/liter	1.8 ± 0.5	1.5 ± 0.5	1.2 ± 0.5		
Calcium, *mg/dl*	9.4 ± 0.8	9.7 ± 1.0	9.8 ± 0.8	NS	NS
mmol/liter	2.4 ± 0.2	2.4 ± 0.2	2.5 ± 0.2		
Alkaline phosphatase, *U/liter*	114 ± 59	123 ± 59	136 ± 81	NS	NS
CO_2 combining power, *mEq/liter*	24.8 ± 3.4	25.3 ± 2.0	21.3 ± 3.4	NS	0.0001
Albumin, *g/dl*	3.18 ± 0.44	3.19 ± 0.41	3.34 ± 0.43	NS	NS (0.063)
Transferrin, *mg/dl*	213 ± 60	225 ± 60	249 ± 72	NS	0.022
Total protein, *g/dl*	5.89 ± 0.57	5.97 ± 0.50	6.27 ± 0.76	NS	0.033
Triglycerides, *mg/dl*	160 ± 101	151 ± 68	174 ± 92	NS	0.023
Total cholesterol, *mg/dl*	203 ± 59	196 ± 60	196 ± 51	NS	NS
HDL cholesterol, *mg/dl*	41 ± 13	44 ± 14	40 ± 9	NS	0.0065
LDL cholesterol	126 ± 48	122 ± 51	122 ± 45	NS	NS
Apolipoprotein B, *mg/dl*	92 ± 42	84 ± 35	90 ± 41	NS	NS

[a] Blood obtained before breakfast at the beginning of the first day of study; [b] Blood obtained before breakfast on day 16 (prior to first exchange with amino acid dialysate); [c] Blood obtained before breakfast on day 36 (last day of study).

patients, diabetes mellitus in two patients, hypertensive nephrosclerosis in two patients, and lupus nephritis, interstitial nephritis, polycystic kidney disease, Alport's syndrome, congenital hypoplastic kidneys, and unknown etiology each in one patient. The patient with lupus nephritis manifested no systemic activity at the time of the study. Seven of the 19 patients were anuric; the creatinine clearances in the other 12 patients averaged 3.0 ± 1.4 ml/min (range, 0.1 to 5.0). Kt/Vurea during the last eight days of the Baseline and Treatment Phases was not different and averaged 1.53 ± 0.36 and 1.61 ± 0.46, respectively.

During the Baseline Phase there was a significant fall in serum urea and creatinine (Fig. 1, Table 2), which may indicate that the patients' hospital protein diet was lower than their prestudy intake or that in the hospital they were more compliant to the dialysis regimen. After commencing the intraperitoneal amino acid treatment, serum urea rose rapidly, but serum creatinine did not change. Serum calcium, alkaline phosphatase, total cholesterol, LDL cholesterol and apolipoprotein B levels did not change during the study (Table 2). Serum potassium ($P = 0.031$) and HDL cholesterol ($P < 0.01$) fell slightly during the treatment period. On the other hand, serum phosphorus fell progressively, from 5.6 mg/dl at the onset of study to 3.8 mg/dl on Day 36. Also, serum triglycerides rose from 151 ± 68 to 174 ± 92 ($P = 0.023$) during the Treatment Phase (Table 2).

Serum albumin, transferrin and total protein did not change during Baseline (Table 2, Fig. 2). After institution of dialysate with amino acids, serum transferrin and total protein rose significantly, whereas serum albumin did not change ($P = 0.063$).

Plasma amino acids obtained before breakfast after an overnight fast are shown in Table 3. Fasting plasma amino acids, obtained from normal men and women from two separate laboratories are shown for comparison. Median ages (and sample sizes) of the subjects in these two populations were 25 years ($N = 12$) (University of Iowa Central Amino Acid Laboratory) and 50 years (range, 32 to 67; $N = 29$) [25], respectively. Since the

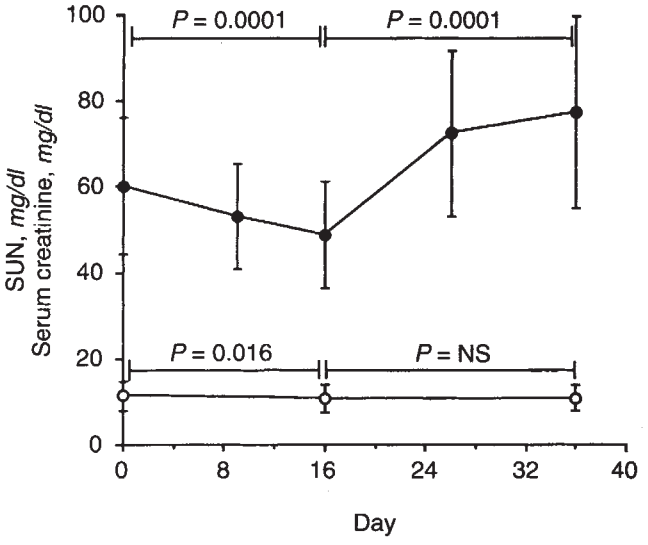

Fig. 1. *Serum urea nitrogen (SUN) and serum creatinine in 19 CAPD patients during the Baseline Phase (Days 0 to 16) and during Treatment (Days 16 to 36) with a dialysate that contained amino acids.* Circles and brackets indicate the mean ± standard deviation. Symbols are: (●) SUN; (○) serum creatinine.

specimens from normal individuals were not obtained during the present study and only one of the groups of normal subjects was analyzed in the laboratory used in the present study, no statistical comparisons between the normal values and the peritoneal dialysis patients were performed.

At the end of Baseline (day 16), as compared to the day of onset of the study (day 0), there was a significant increase in the postabsorptive plasma total essential amino acids, total nonessential amino acids, and total amino acids which persisted throughout

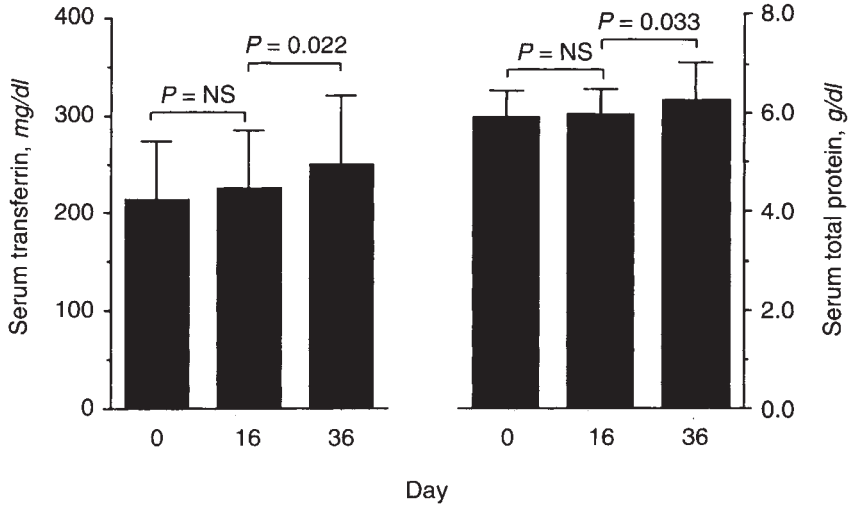

Fig. 2. *Serum transferrin and total protein concentrations in 19 CAPD patients at the beginning (Day 0) and end (Day 16) of the Baseline Phase and at the beginning (Day 16) and end (Day 36) of the Treatment with a dialysate that contained amino acids.* Brackets indicate the mean value plus one standard deviation.

the Treatment Phase. However, only three individual amino acids increased significantly, and ornithine fell slightly at day 16 as compared to day 0. During dialysis with amino acids, at both days 26 and 35, plasma total essential and total amino acids were significantly greater than the values both at the onset of the study (day 0) and at the end of Baseline (day 16). Plasma total nonessential amino acids were not different during the Treatment Phase as compared to the end of Baseline. Many individual amino acids were significantly increased during the Treatment Phase as compared to either the beginning or the end of the Baseline Phase (Table 3). No amino acid was significantly lower during the Treatment Phase than at the beginning of Baseline (day 0), and only plasma taurine was significantly lower at day 26 or 35 as compared to day 16. Virtually all of the increases in the plasma amino acids that occurred during dialysis with amino acids were present at day 26. Only plasma cystine was significantly higher and taurine significantly lower at day 35 as compared to day 26.

The nitrogen balance data are shown in Table 4. Dietary nitrogen intake averaged 8.45 g/day (range 5.8 to 11.0 g/day), which is equivalent to 52.8 g protein/day or 0.80 ± 0.09 g protein/kg body wt/day. Some patients lost a small amount of dietary nitrogen as emesis or uneaten food (Table 4); these losses appeared to increase slightly after the intraperitoneal amino acids were initiated. During the Treatment Phase, the nitrogen intake increased by 47.5 ± 15% due to the instillation of intraperitoneal amino acids. The major route of nitrogen output was dialysate, which increased by approximately 50% with the institution of intraperitoneal amino acids. There was a trend for urine nitrogen to increase slightly when the dialysate with amino acids was instituted (1.5 ± 1.3 vs. 1.3 ± 1.1 g N/day in the Baseline Phase, $P = 0.083$). On the other hand, there was no change in fecal nitrogen output during the study.

During the last 10 days of the Baseline Phase, nitrogen balance, adjusted for changes in body urea nitrogen, was similar during the two balance periods, indicating that the patients had essentially attained a steady state. Nitrogen balance was not different from zero during these two periods. After intraperitoneal amino acids were initiated, nitrogen balance became strongly positive and remained positive for the duration of the study. Although nitrogen balance tended to become less positive with time during the Treatment Phase, it remained significantly greater than zero during each of the three balance periods (Table 4). It may be estimated that between 0.50 and 1.0 g of nitrogen was lost each day from the body from unmeasured sources including respiration, growth of integumentary structures (epidermis, nails, hair), sweat, flatus and the regeneration of protein and amino acids lost from blood drawn [26]. If either of these amounts of nitrogen are added to the total nitrogen output, the average nitrogen balance would still not differ from zero during each of the two balance periods in the Baseline Phase and would still be significantly positive during each of the three balance periods in the Treatment Phase.

Nitrogen balances were significantly more positive during Period 5 as compared to Period 2 ($P < 0.001$), during Period 6 as compared to Period 3 ($P < 0.006$), and with the average of the three Treatment Phase periods (5 to 7) (+1.71 ± 2.40 g/day) as compared to the mean of the two Baseline Phase periods (2 and 3) (+0.50 ± 1.85 g/day) (Treatment vs. Baseline, $P < 0.001$, Table 4). Nitrogen balance, when expressed per kg body weight and averaged for all of the periods of each phase of the study, was also significantly positive during Treatment (+0.0405 ± 0.0520 g/kg/day, $P < 0.01$) but not during Baseline (+0.0092 ± 0.0270 g/kg/day) and was significantly more positive during Treatment as compared to Baseline ($P = 0.001$).

The protein turnover data, calculated from the ^{15}N-glycine studies, are shown in Table 5. Data are available from 16 patients who were each studied twice, once during Baseline and once during Treatment. Total body protein flux tended to increase during the Treatment Phase. There was no significant difference during Treatment as compared to Baseline with regard to protein synthesis or degradation. Protein balance, calculated as total body protein synthesis minus degradation, was positive in both the Baseline Phase (0.24 ± 0.18 g protein/kg/day, $P < 0.001$) and with intraperitoneal amino acids (0.35 ± 0.23, $P < 0.001$). However, net protein anabolism was significantly more positive during the Treatment Phase than during Baseline (Treatment vs. Baseline, $P < 0.001$).

Unlike the nitrogen balances measured in all patients (Table 4), the nitrogen balances depicted in Table 5 were significantly

Table 3. Pre-exchange morning fasting plasma amino acids[a]

	Onset of Baseline	End of Baseline	Dialysis with 1.1% amino acids		Normal values	
	Day 0[b]	Day 16	Day 26	Day 36	$N = 12$[c]	$N = 29$[d]
Essential						
Histidine	64 ± 13[c,f]	64 ± 10	76 ± 14[k,o]	75 ± 13[k,o]	79 ± 19	88 ± 10
Isoleucine	54 ± 14	57 ± 14	60 ± 10[l]	56 ± 11	78 ± 27	64 ± 16
Leucine	79 ± 24	84 ± 19	89 ± 18[l]	89 ± 21	129 ± 36	127 ± 27
Lysine	139 ± 32	159 ± 34[k]	173 ± 39[l,m]	174 ± 31[l,m]	175 ± 45	197 ± 38
Methionine	20 ± 4	23 ± 10	22 ± 4	23 ± 4[j]	33 ± 6	28 ± 5
Phenylalanine	52 ± 18	55 ± 17	54 ± 21	56 ± 16	49 ± 8	56 ± 9
Threonine	107 ± 37	116 ± 35	132 ± 36[k,n]	136 ± 40[k,m]	155 ± 51	155 ± 41
Valine	133 ± 34	138 ± 29	187 ± 30[l,o]	186 ± 42[l,o]	212 ± 74	232 ± 51
Total essential[g]	647 ± 137	683 ± 96[j]	781 ± 81[l,n]	794 ± 114[l,n]	966 ± 211	945 ± 150
Semi-essential						
Cystine	57 ± 23	56 ± 20	63 ± 20[j,o]	69 ± 23[k,o,p]	45 ± 8	61 ± 10
Tyrosine	33 ± 9	34 ± 11	35 ± 12	34 ± 8	55 ± 13	62 ± 13
Non-essential						
Aminobutyrate	6 ± 3	7 ± 5	11 ± 4[k]	10 ± 6	19 ± 8	NA
Alanine	345 ± 122	394 ± 136[k]	402 ± 128[k]	414 ± 155[k]	395 ± 77	433 ± 116
Arginine	74 ± 23	80 ± 21	95 ± 23[k,n]	93 ± 19[l,n]	98 ± 19	99 ± 22
Asparagine	41 ± 10	44 ± 11	44 ± 11	45 ± 10[j]	49 ± 18	48 ± 13
Aspartic Acid	14 ± 7	13 ± 5	16 ± 6	14 ± 7	13 ± 1	6 ± 3
Citrulline	88 ± 29	89 ± 26	98 ± 26[k,n]	98 ± 29[j,n]	29 ± 10	39 ± 12
Glutamic Acid	43 ± 25	50 ± 20	40 ± 19	46 ± 26	37 ± 14	46 ± 22
Glutamine	651 ± 94	671 ± 135	689 ± 123	660 ± 92	540 ± 90	480 ± 133
Glycine	304 ± 98	330 ± 110	288 ± 102	318 ± 119	240 ± 53	265 ± 118
Hydroxyproline	37 ± 14	36 ± 11	33 ± 13	35 ± 13	17 ± 9	16 ± 13
Ornithine	62 ± 19	52 ± 12[k]	62 ± 18[m]	59 ± 15[m]	64 ± 24	66 ± 28
Proline	187 ± 70	186 ± 44	203 ± 47[m]	205 ± 54[m]	187 ± 54	210 ± 65
Serine	67 ± 14	68 ± 18	71 ± 14	71 ± 12	110 ± 28	108 ± 24
Taurine	47 ± 17	67 ± 30[k]	55 ± 23[m]	45 ± 20[o,p]	47 ± 10	48 ± 18
Total nonessential[h]	1773 ± 324	1876 ± 323[j]	1885 ± 274[j]	1911 ± 357[j]	1707 ± 231	1850 ± 378
Total amino acids[i]	2510 ± 393	2649 ± 368[k]	2766 ± 312[l]	2808 ± 418[k,m]	2673 ± 222	2933 ± 514

[a] Blood was drawn before breakfast after an overnight fast several minutes after the abdomen was drained of dialysate and before the early morning dialysate infusion; [b] Before breakfast at the beginning of the first day of study; [c] Normal data from the Central Amino Acid Laboratory, University of Iowa (used by permission); [d] Normal data from the Central Amino Acid Laboratory, Harbor-UCLA Medical Center [25]; [e] Mean ± standard deviation (μmol/liter); [f] Number of patients was 18 on Days 0 and 36 and 19 on Days 16 and 26. Statistical comparisons were made on paired samples for the 18 patients in whom data were obtained for all 4 days; [g] Calculated as the sum of histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, and valine; [h] Calculated as the sum of alanine, arginine, asparagine, aspartic acid, glutamic acid, glutamine, glycine, proline, serine, and taurine; [i] Calculated as the sum of total essential amino acids, total nonessential amino acids, cystine, and tyrosine; [j,k,l] Differs from Day 0, $P < 0.05$, $P < 0.01$, $P < 0.001$, respectively; [m,n,o] Differs from Day 16, $P < 0.05$, $P < 0.01$, $P < 0.001$, respectively; [p] Differs from Day 26, $P < 0.05$.

positive during Baseline as well as during Treatment. This apparent discrepancy may reflect the fact that only 16 of the 19 patients underwent the protein turnover studies, and the nitrogen balances data were only analyzed for eight days with each study. Moreover, if balances are adjusted for estimated unmeasured nitrogen losses of either 0.5 or 1.0 g/day [26], nitrogen balances would still be neutral during Baseline and significantly positive during Treatment. Also, in the data shown in Table 5, nitrogen balance during Treatment continued to be significantly more positive than during Baseline.

Serum carbon dioxide combining power remained stable during Baseline (Table 2). It then decreased significantly from 25.2 ± 2.0 mEq/liter at the end of Baseline to 21.3 ± 3.4 on Day 35 (Day 35 vs. Day 16, $P < 0.001$). This fall in serum carbon dioxide combining power during dialysis with amino acids became apparent after several patients had completed this clinical trial. Consequently, in seven of the patients who entered the program after this trend was observed, arterialized venous blood pH and pCO_2 were measured four times (Fig. 3). The arterialized venous blood pH and pCO_2 fell slightly but significantly after commencing dialysis with amino acids. The blood pH decreased from 7.40 ± 0.03 on both days 5 and 10 to 7.36 ± 0.04 on day 25 and 7.35 ± 0.04 on day 33. On these four days, the pCO_2 was 44.6 ± 5.7, 44.8 ± 3.4, 40.3 ± 6.1 and 38.1 ± 7.0 mm Hg, respectively.

In general, dialysis with the amino acid solution was well tolerated. Of the 19 patients who completed the study, three patients had nausea during the Baseline Phase with glucose dialysate and two patients vomited. By contrast, five patients had episodes of nausea during the Treatment Phase, and two patients vomited during treatment with amino acids. One patient receiving two exchanges per day experienced nausea without emesis on day 20 only (Treatment Phase) that was thought to be caused by uremia; his treatment was not changed because his symptoms abated. Only one of the nine patients that received two amino acid dialysate exchanges per day was unable to tolerate this regimen. She had eight episodes of nausea and vomiting during treatment with intraperitoneal amino acids. On day 24 her SUN was 102 mg/dl, and her regimen was reduced from two amino acid

Table 4. Nitrogen balance data in 19 malnourished CAPD patients (g N/day)

Period	Period days	N intake *g/day*				N output *g/day*					N Balance g/day[e]
		Diet	Emesis or uneaten food	Dialysate	Total intake[a]	Dialysate	Urine[b]	Feces	Δ Body urea N[c]	Total output[d]	
Baseline Phase											
2	6–10	8.47 ± 1.30[f]	0.15 ± 0.49	0	8.32 ± 1.01	6.00 ± 1.59	0.83 ± 1.03	1.17 ± 0.49	−0.05 ± 0.35	7.95 ± 1.94	+0.37 ± 1.83
3	11–15	8.34 ± 1.24	0.02 ± 0.10	0	8.32 ± 1.01	5.90 ± 1.53	0.89 ± 1.16	1.05 ± 0.35	−0.18 ± 0.50	7.66 ± 2.09	+0.62 ± 1.85
Mean											+0.50 ± 1.85
Treatment Phase											
5	21–25	8.34 ± 1.19	0.06 ± 0.19	4.92 ± 1.59	13.19 ± 2.32	8.31 ± 2.16	0.95 ± 1.17	1.11 ± 0.51	+0.66 ± 0.53	11.01 ± 2.82	+2.15 ± 2.35[g,h]
6	26–30	8.30 ± 1.16	0.09 ± 0.21	4.87 ± 1.55	13.09 ± 2.24	8.95 ± 2.57	1.04 ± 1.35	0.97 ± 0.47	+0.38 ± 0.38	11.34 ± 3.00	+1.61 ± 2.42[g,i]
7	31–35	8.16 ± 1.27	0.26 ± 0.53	4.73 ± 1.56	12.63 ± 2.31	9.03 ± 2.73	1.06 ± 1.39	1.15 ± 0.46	−0.01 ± 0.49	11.23 ± 3.06	+1.38 ± 2.46[g]
Mean											+1.71 ± 2.40[g,j]

[a] Calculated as the sum of diet and dialysate nitrogen minus emesis nitrogen; [b] Average values, some patients were anuric; [c] An increase and decrease in body urea nitrogen is indicated by a plus and minus sign, respectively; [d] Calculated as the sum of dialysate, urine, feces and change in body urea nitrogen; [e] Calculated as total intake minus total output of nitrogen; [f] Mean ± standard deviation; [g] Significantly different from zero, $P < 0.001$; [h] Significantly different from nitrogen balance in period 2, $P < 0.001$; [i] Significantly different from nitrogen balance in period 3, $P < 0.001$; [j] Mean of nitrogen balances in periods 5, 6, and 7 is significantly different from mean of balances in period 2 and 3, $P < 0.001$.

Table 5. Protein turnover before and during treatment with intraperitoneal amino acids[a]

	Patient No.	Body weight *kg*	N balance[c] *g/kg/day*	Flux	Protein metabolism, *g protein/kg/day*		
					Synthesis	Degradation	Net anabolism
Baseline Phase	16	68.7 ± 11.8[d]	+0.022 ± 0.028[e]	2.80 ± 0.06	2.25 ± 0.59	2.01 ± 0.65	+0.24 ± 0.18[f]
Treatment Phase	16	69.0 ± 12.0	+0.040 ± 0.035[f]	3.29 ± 1.01	2.49 ± 0.97	2.14 ± 1.00	+0.35 ± 0.23[f]
P values (Treatment vs. Baseline[g])		NS	$P = 0.002$	NS ($P = 0.063$)	NS	NS	$P = 0.001$

[a] Data collected during Days 8-15 of Baseline Phase and during Days 26 to 33 of Treatment Phase; [b] Weight on day that ^{15}N-glycine was ingested; [c] Refers to N balance measurements during the period of the protein turnover studies; [d] Mean ± standard deviation; [e] Significantly different from zero, $P < 0.01$; [f] Significantly different from zero, $P < 0.001$; [g] P values determined by the paired *t*-test.

exchanges per day to one. Her SUN declined to 92 mg/dl by Day 26 and to 82 mg/dl by Day 36. Nausea and vomiting slowly abated after she began one exchange with amino acids per day.

Discussion

The results of this study indicate that chronic peritoneal dialysis patients who have protein or protein calorie malnutrition and are ingesting a low protein diet develop positive protein balance when they receive dialysate containing amino acids. The evidence that intraperitoneal amino acids enhance their anabolic status includes a significant increase in nitrogen balance, greater net protein anabolism, as determined by ^{15}N-glycine turnover studies, and an increase in serum transferrin and total protein concentrations. Serum albumin levels also tended to rise with the intraperitoneal amino acids, but the increase was not statistically significant ($P < 0.07$). There was an increase in fasting plasma total essential and total amino acids as well as of a number of individual amino acids. The rise was particularly evident for the essential amino acids (Table 3).

Other researchers have investigated the nutritional benefits of peritoneal dialysate containing amino acids. In several studies, a significant increase in serum albumin or transferrin [12, 15, 18, 19], estimated nitrogen balance [14, 20], total body nitrogen [12], or body weight [14, 19] was reported. On the other hand, some studies showed no significant improvement in these nutritional parameters [17], and in a number of studies not all nutritional parameters increased. Moreover, in one of the two studies showing a rise in serum albumin during the treatment with amino acids in peritoneal dialysate, it was not sustained [18]. Interpretation of these results is complicated by the fact that simultaneous, randomized control groups were generally not used, normal nutritional status was usually not a patient exclusion criterion, the sample sizes were small, and dietary nutrient intake often was not controlled or monitored. In the present study, although a separate group of control patients was not used, the abrupt increase in the anabolic status of the patients after Baseline, when treatment with dialysate containing amino acids was inaugurated, provides strong evidence that the enhanced protein balance of the patients was due to the intraperitoneal amino acids.

In one small controlled study, Renzo treated four diabetic CAPD patients with one exchange per day of 1% intraperitoneal amino acids for 9 to 17 months [19]. A similar group of four diabetic patients served as controls. All patients initially had low serum albumin concentrations. After treatment for an average of 12 months, the serum albumin rose significantly, by 0.7 g/dl, in the amino acid treated group and did not change in the controls. Moreover, the insulin dosage decreased only in the amino acid treatment group. In a study by Dombros et al, the intraperitoneal

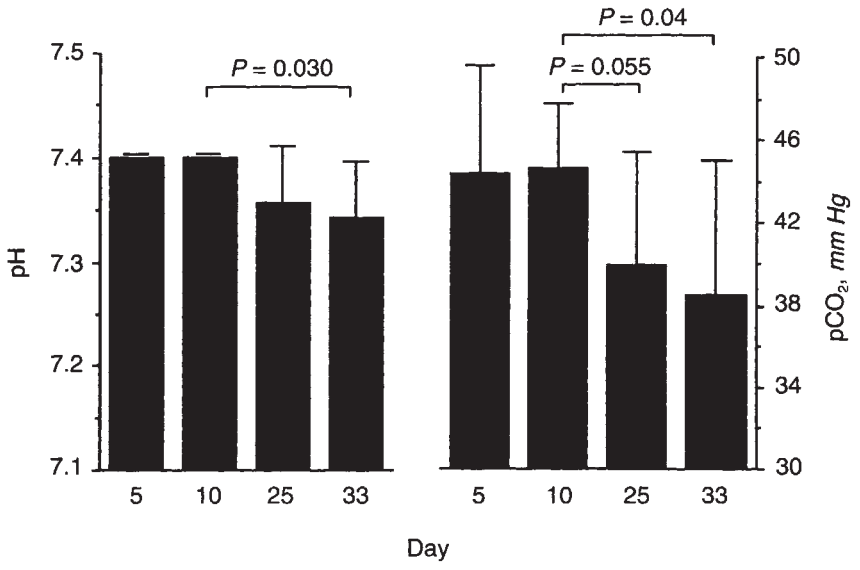

Fig. 3. *Arterialized venous blood pH and $pC0_2$ in seven CAPD patients at the indicated time points during the study.* Brackets indicate the mean value plus one standard deviation.

amino acids were given in the overnight exchange with no apparent beneficial effects [17]. The lack of a concurrent intake of calorie sources and other nutrients might have impaired the anabolic effects of the intraperitoneal amino acids in these patients.

The use of amino acids as a substitute for dextrose has been proposed as a method for reducing hyperlipidemia in chronic dialysis patients by decreasing the glucose load [27]. The replacement of glucose with amino acids in one or at most two dialysate solutions would be expected to decrease glucose absorption by only about 20 to 40 g/day of anhydrous D-glucose [28]. This estimate assumes that the 1.1% amino acid solution is substituted for 1.5% dextrose (1.36% anhydrous glucose), which has a similar tonicity. Moreover, the dextrose solution would be expected to elicit a hyperinsulinemic response and this might also diminish with an amino acid exchange, thereby reducing lipogenesis and serum lipid concentrations. However, many of the intraperitoneal amino acids absorbed may be converted to glucose and also may stimulate insulin secretion.

Published experience with the dialysate amino acid solutions indicates that serum lipids generally do not fall significantly [12, 13, 17–19]. Two studies report a decrease in serum cholesterol [14, 15]. One of these reports also described a fall in serum triglycerides [14], whereas in another study, the serum triglycerides rose [13]. In the present study, serum total cholesterol, HDL cholesterol, LDL cholesterol and apolipoprotein B did not change with the intraperitoneal amino acid treatment, although serum triglycerides rose significantly (Table 2). The cause for the rise in serum triglycerides is unclear. The patients' dietary protein intake during the study was similar to their prestudy intake (Tables 1 and 3). However, despite our efforts to design an intake similar to the prestudy diet, the energy intake during the study may have been greater. If it was, this could account for the rise in serum triglycerides, which appeared to have begun during the Baseline Phase (Table 2).

In the current study, patients appeared to develop a mild metabolic acidosis when they were given intraperitoneal amino acids (Table 2, Fig. 3). This was evidenced by a decrease in serum carbon dioxide combining power and in the arterialized venous blood pH and $pC0_2$. The anion gap rose slightly with the intraperitoneal amino acids, from 12.8 to 14.2 mEq/liter, although the rise was slightly less if serum potassium concentrations were included in the calculations (that is, from 17.0 to 18.1 mEq/liter). The fall in serum carbon dioxide combining power also was partly due to a rise in serum chloride, from 95 to 98 mEq/liter. The acidemia was greater with two amino acid exchanges than with one exchange. Other researchers have also described the development of mild acidemia with intraperitoneal amino acids [14, 15, 18]. They have attributed the acidemia to the acid load delivered by the hydrochloride salts of certain basic amino acids as well as to an increase in the anion gap caused by the metabolism of the absorbed amino acids.

In the present study, the hydrochloride salt of lysine was employed in the dialysate containing amino acids. The finding that there was a slight increase in both the serum chloride and anion gap suggests that both the hydrochloride salt of lysine and the generation of acids from the amino acids contributed to the acidemia. The largest component of the increment in the anion gap was probably due to sulfate formed by the oxidation of the sulfur in dialysate methionine. Since even mild degrees of acidemia may promote protein catabolism [29], it is important to prevent the acidemia. This may be possible to achieve by giving patients small amounts of alkalinizing agents to ingest. In the future it should be possible to increase the lactate and reduce the chloride concentrations in the dialysate. It is possible that the anabolic response to intraperitoneal amino acids in our patients would have been even greater if the patients had not become acidemic.

Some, but not all studies, indicate that intraperitoneal amino acids increase peritoneal protein losses [14, 16, 30, 31]. In the present study no significant increase in peritoneal protein losses was observed over the 20 days that patients received the amino acids (data not shown).

Several postabsorptive (overnight fasting) plasma amino acid levels became more normal with the intraperitoneal amino acid treatment (Table 3). This was particularly evident for histidine, lysine, threonine, valine, total essential amino acids, alanine and

arginine. Almost all of the changes in plasma amino acids that occurred with the intraperitoneal amino acids were present by the tenth day of treatment (day 26). This is not surprising since in protein depleted non-uremic individuals ingesting low protein diets, low plasma amino acid concentrations generally rise within several days in response to a high protein diet [32]. With the intraperitoneal amino acid treatment, there was an increment in the preexchange fasting plasma cystine levels, which were not low during Baseline. This may have been caused by the load of the cystine precursor, methionine, in the dialysate. In the current study, postabsorptive plasma methionine levels were normal (Table 3), although the postexchange plasma methionine was slightly elevated (data not shown).

The finding that postabsorptive cystine also rose during the Treatment Phase suggests that the dialysate methionine concentrations possibly should be reduced further. On the other hand, the finding that plasma taurine fell and plasma cysteine rose during treatment also raises the possibility of a metabolic block in the synthesis of taurine from cystine. The fall in plasma taurine during intraperitoneal amino acid treatment is puzzling. Although the mean plasma taurine levels during the intraperitoneal amino acid treatment were within the normal range (Table 3), plasma taurine concentrations in some patients were clearly low. Contamination of plasma with platelets may raise plasma taurine concentrations [33]. It is possible that this contributed to the higher taurine levels on day 16, although it is not clear how greater plasma contamination would occur in all centers on day 16 and possibly on day 26 (Table 3). The rise in the three urea cycle amino acids, arginine, citrulline and ornithine, may reflect the larger amino acid load and, hence, augmented urea generation during the intraperitoneal amino acid treatment.

In summary, the present study indicates that one or two peritoneal dialysate exchanges per day containing a 1.1% solution of essential and nonessential amino acids induced a clear anabolic response in a group of malnourished CAPD patients who were ingesting rather low amounts of protein. The intraperitoneal amino acids were usually well tolerated, although a mild metabolic acidemia, which should be readily treatable, occurred in some individuals.

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