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Long-term effects of a new ketoacid–amino acid supplement in patients with chronic renal failure

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Long-term effects of a new ketoacid–amino acid supplement in patients with chronic renal failure. Nine patients with severe chronic renal failure (mean glomerular filtration rate 4.8 ml/min; mean serum creatinine 11.3 mg/dl) who were previously on a protein-restricted diet were treated with a diet containing an average of 33 kcal/kg and 22.5 g/day of mixed quality protein, supplemented by a combination of amino acids and mixed salts formed between basic amino acids and keto-analogues of essential amino acids. The supplement was designed to minimize or reverse the amino acid abnormalities of chronic renal failure rather than to meet the normal requirements for the essential amino acids; it contained tyrosine, ornithine, and a high proportion of branched-chain ketoacids, but no phenylalanine or tryptophan and very little methionine. Within one month, serum urea nitrogen fell and serum albumin and transferrin rose significantly; serum creatinine fell slightly. Hyperphosphatemia (present in three patients) was corrected. Nitrogen balance, measured in seven of the nine patients, on the average was neutral, as it was in a preceding control period on a 40 to 50 g/day protein diet. Plasma tyrosine and threonine, which were subnormal before therapy, rose to normal or high normal levels. Branched-chain amino acids did not change. During a total of 63 patient-months of therapy, no side effects or toxicity were observed, and serum albumin and transferrin did not change further. It is concluded that this specially designed supplement added to a 20 to 25 g/d protein diet is an acceptable regimen which can improve or maintain protein nutrition in patients with severe chronic renal failure who would otherwise require dialysis.

Effet à long terme d'un nouveau mélange de cétoacides – d'amino acides chez des malades ayant une insuffisance rénale chronique. Neuf malades ayant une insuffisance rénale chronique sévère (filtration glomérulaire moyenne 4,8 ml/mn, créatininémie moyenne 11,3 mg/dl) recevant préalablement un régime pauvre en protéines, ont été traités avec un régime apportant en moyenne 33 kcal/kg et 22,5 g/j de protéines mixtes, auquel a été ajouté un mélange d'acides aminés et de sels d'acides aminés basiques et de céto-analogues d'acides aminés essentiels. Ce supplément a été conçu plus pour diminuer ou supprimer les anomalies des acides aminés au cours de l'insuffisance rénale chronique que pour fournir les besoins normaux en acides aminés essentiels; il contenait de la tyrosine, de l'ornithine et une grande proportion de cétoacides à chaînes ramifiées, mais ni phénylalanine, ni tryptophane, et très peu de méthionine. En moins d'un mois, l'azote uréique plasmatique a baissé; la sérum albumine et la transférine se sont élevées significativement, la créatininémie a légèrement diminué. L'hyperphosphatémie (présente chez trois malades) a été corrigée. La balance azotée, mesurée chez sept des neuf malades était nulle en moyenne, comme elle l'était au cours de la période contrôle précédente, avec un régime comportant 40 à 50 g/j de protéines. La tyrosine et la thréonine plasmatiques, inférieures à la normale avant traitement, se sont normalisées, ou ont atteint des valeurs à la limite supérieure de la normale. Il n'y a pas eu de modification des concentrations d'acides aminés à chaînes ramifiées. Pendant un traitement durant au total 63 mois-malade, il n'a pas été observé d'effet secondaire ni de toxicité, et il n'y a pas eu d'autre modification de l'albumine ou de la transferrine plasmatique. Il est conclu que ce mélange spécialement conçu, rajouté à un régime apportant 20 à 25 g/j de protéines constitue un régime acceptable, permettant d'améliorer ou de maintenir l'apport protidique chez des malades ayant une insuffisance rénale chronique sévère qui, autrement, nécessiteraient la dialyse.

The dietary requirements for amino acids of patients with chronic renal failure (CRF) are unknown but are likely to differ from those of normal subjects, for two reasons. First, multiple abnormalities of amino acid concentrations in plasma and intracellular water of muscle are seen in uremia [1]. Second, several specific defects in amino acid metabolism have been identified in renal failure, including impaired conversion of citrulline to arginine [4], impaired hydroxylation of phenylalanine [5–9], accelerated destruction of valine [10], and altered protein-binding of tryptophan [11].

Attempting to achieve normal plasma or intracellular concentrations of amino acids is one method of judging the adequacy of dietary amino acid supplements; assessing protein nutrition is another method. For uremic subjects, it is especially important to ensure that the total intake of amino acids is sufficient to maintain nitrogen equilibrium, but not excessive, which would lead to unnecessary accumulation of waste nitrogen. One means of achieving this goal is to supply a portion of daily essential amino acid requirements as nitrogen-free amino acid analogues [12, 13].

Several studies have documented the efficacy of supplements containing nitrogen-free analogues of the branched-chain amino acids, phenylalanine and methionine, plus the remaining essential amino acids, when added to a diet adequate in calories and containing 20 to 25 g of protein unrestricted as to quality [13]. The acceptability of this diet appears to be greater than that of a 40 g protein diet containing predominantly high quality protein [14].

The analogue supplements used in these studies usually contained a relatively high proportion of the branched-chain ketoacids, because these compounds are known to be decarboxylated oxidatively to some extent in the liver [15]. In other respects, the proportions of the individual components have been based on requirements for normal subjects. Moreover, the

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Table 1. Initial characteristics of patients and duration of therapy

Patient	Sex	Age *years*	Diagnosis[a]	Glomerular filtration rate[b] *ml/min*	Serum values		Months of treatment
					Urea N	Creatinine *mg/dl*	
1	F	60	GN	2.9	106	15.5	17
2	F	43	PC	3.5	105	11.6	7
3	M	78	GN	4.0	98	10.6	4
4	F	55	GN	5.1	96	11.0	13
5	M	51	DN	3.3	114	14.0	4
6	M	74	HN	5.2	126	9.5	4
7	M	48	HN	6.1	91	10.2	7
8	M	72	DN	7.0	79	6.8	3
9	M	49	HN	6.5	82	10.5	4
Mean				4.8	100	11.3	7.0
SEM				±0.5	±5	±0.9	—

[a] Abbreviations: GN, glomerulonephritis; PC, polycystic kidney disease; DN, diabetic nephropathy; HN, arteriolar nephrosclerosis; and N, nitrogen.

[b] Glomerular filtration rate was estimated as the average of 24-hr creatinine and urea clearances.

Table 2. Composition of mixture "EE"

Compound	Dose	
	mmoles/day	*mg N/day*
L-tyrosine	20	280
L-threonine	15	210
L-ornithine α-ketoisovalerate	7	196
L-ornithine α-ketoisocaproate	7	196
L-ornithine R,S-α-keto-β-methylvalerate	7	196
L-lysine α-ketoisovalerate	7	196
L-lysine α-ketoisocaproate	7	196
L-lysine R,S-α-keto-β-methylvalerate	7	196
L-histidine α-ketoisocaproate	4	112
Calcium D, L-α-hydroxy-γ-methiolbutyrate	2	0
Total	*83*	*1778*

analogues have been provided as calcium salts, which probably account for the occasional occurrence of hypercalcemia reported in some studies [16–18], though not in all [13], and perhaps for occasional gastrointestinal distress occurring at the start of therapy [1].

Recently, we described the characteristics of mixed salts formed between basic amino acids and branched-chain ketoacids and preliminary results of the use of these salts in an analogue supplement [19]. Based on those data, we have designed an analogue supplement that includes these salts, a small amount of methionine (as its hydroxy analogue), and tyrosine but devoid of phenylalanine or tryptophan in any form. This supplement was given to patients with CRF, and its effectiveness was tested during long-term administration.

Methods

Three women and six men with severe chronic renal failure were studied after obtaining informed consent. Characteristics of these patients and duration of treatment are shown in Table 1. The composition of the mixture of amino acids and nitrogen-free analogues is shown in Table 2. The doses of the keto-analogues of the branched-chain amino acids are increased above "normal" requirements for the respective amino acids, and the mixture contains tyrosine, but no tryptophan or phenylalanine; only a small quantity of the hydroxy-analogue of methionine is included as the calcium salt. The chemical characteristics of the mixed salts used are described elsewhere [19].

Nitrogen balance was determined in six patients during two consecutive 5-day periods; first, they consumed a diet with an amount of protein similar to that they had been eating as outpatients (determined by dietary recall); subsequently, their protein intake was lowered to 20 to 25 g/day (average 22.5 g/day), and they were given the analogue supplement. The effects of the control diet were always studied first because there are beneficial effects of α-ketoisocaproate on nitrogen balance that can be detected for as long as 7 days after discontinuing the analogue supplement [20]. Nitrogen balance in a seventh patient was determined only while he received the supplement. The other two patients declined to be admitted to the hospital for balance studies. Caloric content of the diets was 33 ± 3 kcal/kg/day and did not differ significantly between the two balance periods. The patients took 1 mg folic acid and a B vitamin complex tablet daily, and most patients also received supplements of calcium.

Nitrogen balance studies were conducted as previously reported [21]. Balance was calculated as the difference between nitrogen intake (I_N) and the sum of urinary urea nitrogen (UUN), urinary nonurea nitrogen (UNUN), fecal nitrogen (F_N) and the change in the body pool of urea nitrogen (Δ). Changes in this pool were calculated from the ^{14}C urea space, daily measurements of body weight, and daily measurements of serum urea nitrogen concentrations. No correction was made for unmeasured losses of nitrogen. Statistical methods have been reported previously [21].

Before starting the supplement and at 2- to 4-week intervals thereafter, plasma was obtained after an overnight fast and amino acid concentrations were measured by automated ion-exchange chromatography. A total of 16 samples was obtained before treatment, 18 samples during the first month, 13 during the second, and 15 during the third and fourth months. For each

Table 3. Effects of therapy on serum chemical values, means ± SEM

	Initial	4 to 6 weeks	Change	P^a
Urea nitrogen, *mg/dl*	100.0 ± 5.0	87.0 ± 6.0	−12.0 ± 2.0	<0.01
Creatinine, *mg/dl*	11.3 ± 0.9	10.1 ± 0.8	−1.16 ± 0.45	<0.05
Albumin, *g/dl*	3.9 ± 0.1	4.1 ± 0.1	+0.27 ± 0.06	<0.01
Transferrin, *mg/dl*	209.0 ± 22.0	267.0 ± 21.0	+21.0 ± 7.0	<0.02
Calcium, *mg/dl*	9.0 ± 0.3	9.4 ± 0.2	+0.4 ± 0.3	NS
Phosphorus, *mg/dl*	4.9 ± 0.6	3.9 ± 0.2	−1.0 ± 0.6	NS

[a] *P* value from paired comparison.

patient, a mean value at each of these time intervals was calculated. The significance of these changes was evaluated by Student's paired *t* test. Tryptophan could not be reliably measured in these samples.

Serum chemical values were determined before treatment and once or twice a month during treatment. The statistical significance of changes was evaluated at 4 to 6 weeks and then monthly by Student's paired *t* test.

The rate of progression of renal insufficiency was calculated in seven patients by determining the linear regression slope of the reciprocal of serum creatinine concentration against time and the SEM of this slope [22]. In the other two patients, insufficient data before therapy were available to make this calculation.

Results

Serum chemical values. As shown in Table 3, serum urea nitrogen and creatinine fell significantly within 4 to 6 weeks after initiating therapy with the analogue supplement. Serum albumin and transferrin rose significantly. Serum calcium scarcely changed, but phosphate fell from a mean of 4.9 mg/dl to 3.9 mg/dl. Although this latter change is not significant statistically, it is worthy of note that the three patients who had hyperphosphatemia before treatment (patients 1, 3 and 4; average initial phosphate 6.9 mg/dl) became normophosphatemic (average phosphate at 4 to 6 weeks, 3.7 mg/dl). Furthermore, none of the other patients developed hyperphosphatemia or hypophosphatemia. Other serum chemical values, including sodium, potassium, chloride, carbon dioxide, glucose, triglycerides, cholesterol, and uric acid did not change. Alkaline phosphatase increased slightly but insignificantly at 4 to 6 weeks. No further statistically significant changes in any of these values were found in the ensuing months.

Nitrogen balance. As shown in Table 4, nitrogen intake with this regimen was, on the average 1.36 g lower than with the control diet. Urea nitrogen appearance, calculated as the sum of urine urea nitrogen and the rate of change of the body urea nitrogen pool, fell from an average of 4.5 g/day to 3.4 g/day with the analogue mixture ($P < 0.01$). No change occurred in the other components of nitrogen excretion. Thus, the nitrogen contained in feces and urinary nonurea nitrogen ranged from 1.63 to 3.11 gN/day, similar to values we have previously found in patients with chronic renal failure [12, 21, 23, 24].

Nitrogen balance was on the average minimally, but insignificantly, positive in the control period. Because the amount of protein in the control diet was chosen from the dietary record of each patient and because there was little or no indication of protein malnutrition before therapy (Table 3), it is not surprising that nitrogen balance was neutral. When the diet was changed and the analogues were given, nitrogen balance remained neutral; it improved significantly in only one patient (no. 3). If a correction of 0.5 g/day is applied for unmeasured nitrogen losses, balance becomes minimally, but insignificantly, negative during both periods.

The nitrogen balance data indicate that the analogues substituted for dietary essential amino acids, since nitrogen balance becomes negative within 1 to 3 days when a single essential amino acid is omitted from the diet [25]. We have made similar observations in uremic subjects eating virtually protein-free diets [21, 24]. Moreover, the analogue regimen was as effective as the higher protein diet in maintaining long-term protein nutrition since serum concentrations of albumin and transferrin improved slightly (and remained within the normal range) during long-term therapy (Table 3).

Plasma amino acids. Compared to normal subjects [26], these patients exhibited significantly elevated plasma levels of taurine, citrulline, cystine, and 3-methylhistidine, and significantly decreased levels of threonine, serine, valine, isoleucine, leucine, and tyrosine before beginning treatment. These changes are similar to those reported in other series of patients with CRF [1].

During treatment with the supplement, few statistically significant changes in plasma amino acids were observed. Threonine rose significantly during the first, second and third months (+38 ± 10 μM, +89 ± 18 μM and +69 ± 13 μM, respectively). Because mean initial threonine was only 32 μM less than the mean of normal controls, these results suggest that the threonine content of the supplement may have been slightly too high. Alloisoleucine rose by an average of 42 μM. This change occurs regularly in patients given racemic ketoisoleucine [27]. Tyrosine, a component of the supplement, rose from 45 ± 3 μM (normal = 74 ± 4 μM) to 72 ± 9.5 μM at the second month, becoming normal. Lysine, which was normal initially (202 ± 13 μM), rose slightly (+33 ± 10 μM) at the second month, again suggesting that a slightly lower dose might have sufficed. 3-Methylhistidine, which was 46 ± 3 μM initially (normal = 5 ± 1 μM) fell by 9 ± 2 μM after two months. This probably reflects a reduced intake of meat. No other plasma amino acid concentration changed significantly, including those of the branched-chain amino acids, ornithine or histidine.

Progression of renal insufficiency. Despite the fact that the serum creatinine concentration fell by a small, but significant, amount at 4 to 6 weeks, a change in the rate of progression of renal insufficiency could be demonstrated in only one patient (no. 1). The rate of change of reciprocal serum creatinine concentration in this patient during treatment with "EE" was

Table 4. Components of nitrogen balance in patients treated with supplement "EE"[a]

Patient no.	I_N[b] Control	I_N[b] KA[c]	UUN[b] Control	UUN[b] KA	NUUN[b] Control	NUUN[b] KA	F_N[b] Control	F_N[b] KA	I–O[b] Control	I–O[b] KA	Δ[b] Control	Δ[b] KA	b_N[b] Control	b_N[b] KA
	g^N/day		g^N/day		g^N/day		g^N/day		g^N/day		g^N/day		g^N/day	
1	7.05	5.41	4.60	4.17	0.64	0.46	1.00	0.94	+0.82 ±0.14	−0.16 ±0.31	+0.16 ±0.06	−0.37 ±0.15	+0.66 ±0.15	+0.21 ±0.34
2	6.82	5.46	4.13	3.99	1.95	1.53	1.16	0.96	−0.42 ±0.49	−1.02 ±0.32	+0.04 ±0.33	−0.38 ±0.24	−0.46 ±0.59	−0.64 ±0.40
3	6.73	5.65	4.74	3.81	1.09	0.79	1.10	0.72	−0.20 ±0.15	+0.32 ±0.29	−0.49 ±0.32	−1.37 ±0.13	+0.29 ±0.35	+1.69[d] ±0.32
4	6.72	5.28	3.69	3.63	0.53	0.59	1.10	1.15	+1.40 ±0.40	−0.09 ±0.19	+0.32 ±0.20	−0.77 ±0.14	+1.08 ±0.45	+0.68 ±0.24
5	7.44	5.74	5.52	5.73	1.22	1.10	1.10	0.60	−0.40 ±0.37	−1.70 ±0.21	−0.08 ±0.21	−1.75 ±0.34	−0.32 ±0.42	+0.05 ±0.40
6	6.61	5.51	3.26	3.09	1.21	1.54	0.84	1.01	+1.30 ±0.37	−0.13 ±0.26	+1.15 ±0.45	−0.87 ±0.13	+0.15 ±0.58	+0.74 ±0.29
7		5.71		5.66		0.92		0.70		−1.58 ±0.12		−1.13 ±0.22		−0.45 ±0.26
Mean	6.89	5.53[e]	4.32	4.29	1.11	0.99	1.05	0.86	0.42	−0.62[e]	0.18	−0.94[e]	+0.23	+0.32
SEM	±0.12	±0.06	±0.33	±0.38	±0.21	±0.16	±0.05	±0.07	±0.35	±0.30	±0.22	±0.19	±0.24	±0.30

[a] Values are mean ± SEM.
[b] Components of nitrogen balance are: I_N, nitrogen intake; UUN, urinary urea nitrogen; NUUN, nonurea urinary nitrogen; F_N, fecal nitrogen; I–O, intake minus output nitrogen; Δ, rate of change in urea nitrogen pool; b_N, nitrogen balance.
[c] KA represents the results while receiving analogue-based supplement.
[d] Significantly different from zero, $P < 0.05$.
[e] Significantly lower than control by paired comparison in patients 1 to 6, $P < 0.01$.

slower ($P < 0.02$) compared to the rate before therapy. In six others, no change occurred, and in two others, historical data before therapy were insufficient for this type of analysis.

Discussion

All the patients in this study were rapidly approaching the time when dialysis would become necessary. The data presented indicate that this analogue-supplement regimen can forestall the need for dialysis by an average of about 7 months, while maintaining protein nutrition. In fact, nutrition improved, as evidenced by significant increases in serum albumin and transferrin, correction of hyperphosphatemia, and improvement in the plasma amino acid concentration pattern. It should be added also that both the diet and the supplement were well tolerated and readily accepted. To assess compliance, changes in plasma alloisoleucine concentration were calculated because this amino acid is present in trace amounts in the plasma of normal subjects and patients with chronic renal failure, but invariably is found in subjects receiving R,S-α-keto-β-methylvalerate, the ketoanalogue of isoleucine [27]. In the present study no patient had a plasma alloisoleucine level greater than 9 μM before beginning therapy. However, throughout the period of study, alloisoleucine levels were increased in every sample taken and were within the range we have previously found to occur in hospitalized patients receiving this keto-analogue [1]. Others [14] have noted that 20 to 25 g mixed quality protein diets supplemented with a source of essential amino acids are more acceptable to renal failure patients than diets containing 40 g of predominantly high quality protein such as eggs and cottage cheese.

The use of mixed salts formed between basic amino acids and ketoanalogues has several advantages, compared to the calcium salts of keto-analogues that have been studied previously [13]. These mixed salts are more soluble and palatable than the calcium salts and also more soluble than the corresponding branched-chain amino acids themselves [19]. While calcium supplementation has often been advocated in CRF [1], dangers are attendant on its use especially in the presence of hyperphosphatemia [28]. In three studies in which calcium salts of ketoacids were employed, a few patients were reported to develop hypercalcemia [16–18], but this has not been reported in other studies [13]. The extra calcium may also play a role in the gastric distress reported in some patients receiving calcium salts of ketoacids [1]; gastric distress was not a significant complaint of the patients in the present study.

It remains to be determined whether or not this supplement can slow the progression of renal insufficiency if started at a somewhat earlier stage. Barsotti et al [29] have observed a marked reduction in the rate of decline of creatinine clearance in a group of patients with CRF of moderate severity given ketoacids as calcium salts.

In a recent compilation of the results of the plasma concentrations of amino acids in chronic uremic patients, it was pointed out that the concentrations of valine, isoleucine, and leucine are subnormal in almost all reports [1]. In the intracellular water of muscle in uremic adults, the concentration of isoleucine is normal in the absence of severe protein restriction while leucine is somewhat reduced and valine more so [30, 31]. Treatment of chronically uremic adults with a low protein diet and a supplement of essential amino acids containing more leucine than valine and more valine than isoleucine results in a normal or nearly normal plasma level of isoleucine and valine; leucine remains subnormal. This regimen also results in normal levels of branched-chain amino acids in the intracellular water of

muscle [30]. Recently, a supplement containing 40 to 43% less leucine and isoleucine and 18% more valine was given to chronically uremic adults and its effect on plasma and intracellular amino acid concentrations tested [2]. This supplement contained twice as much valine as isoleucine, and isoleucine and leucine were within the normal range as were the intracellular concentrations of all three branched-chain amino acids.

Rat-feeding experiments have shown that higher intakes of leucine impair utilization of valine and isoleucine while high intakes of the latter two amino acids do not impair utilization of leucine except when leucine intake is very low [32]. Thus, if plasma amino acid levels are considered as the criterion of nutritional adequacy of a given supplement, more valine and less leucine and isoleucine should be given. On the other hand, no difference in clinical efficacy was demonstrated between various amino acid supplements despite varying effects on plasma and intracellular amino acid concentrations [2, 30].

It is possible that the failure of plasma branched-chain amino acid concentrations to rise with the present supplement is due to the higher proportion of the keto-analogue of leucine. Administration of this analogue [20, 33] or leucine itself [34–37] results in a decrease in the plasma concentration of isoleucine and valine. However, this analogue has been shown to exert a nitrogen-sparing effect during short-term starvation, an effect not induced by leucine [20]. This may be a factor in the improvement in protein nutrition observed in these patients even though their plasma levels of branched-chain amino acids remained low.

A unique feature of the supplement used in the present study is the absence of tryptophan and phenylalanine in any form; in addition, the proportion of the methionine analogue was very low (about 1% of the total). Nevertheless, the concentrations of phenylalanine and methionine in plasma did not fall. Tryptophan was not measured in this study, but was found not to change in patients given a similar supplement devoid of tryptophan [19]. Nitrogen balance remained essentially neutral despite the "unbalanced" supply of essential amino acids (Table 2) and a diet containing less protein than normal requirements. Moreover, the sustained improvement in serum albumin and transferrin suggests that protein nutrition was maintained during the 63 months of therapy.

Inclusion of ornithine in the supplement may be useful for two reasons. Intracellular ornithine concentration in muscle is subnormal in chronic uremic patients on moderate protein restriction [31]. Secondly, two recent reports [38, 39] have documented mild hyperammonemia in chronic uremia, and ornithine should tend to lower blood ammonia [26].

A comparative study of an analogue-based supplement with an amino acid supplement, both containing tyrosine, arginine or ornithine, and increased quantities of branched-chain compounds (especially valine), would be of interest. To design the supplements to be compared, measurements of the extent of decarboxylation of the branched-chain ketoacids (as compared with the corresponding amino acids) would be helpful. A technique for making such measurements has been described recently [40]. Two other studies in which analogue-based supplements were compared with amino acid supplements, when added to 20 to 25 g protein diets [17, 41] have shown the analogues to be more efficacious. A third study [42] in which nitrogen intake was substantially higher, reported no difference in efficacy. Thus, nitrogen intake may be a critical factor in the design of such studies.

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