

Acta Medica Okayama

Volume 32, Issue 6

1978

Article 7

DECEMBER 1978

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Abstract

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KEYWORDS: serum amino acids, hepatic encephalopathy, liver cirrhosis, fulminant and subacute hepatitis, aromatic and branched chain amino acids

Acta Med. Okayama 32, (6), 427—440 (1978).

**AN APPROACH TO NUTRITIONAL THERAPY OF
HEPATIC ENCEPHALOPATHY BY NORMALI-
ZATION OF DERANGED AMINO ACID
PATTERNS IN SERUM**

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Received July 14, 1978

Abstract. A mixture with essential and nonessential amino acids high in branched chain amino acids and low in aromatic amino acids (Fischer solution), and another synthetic mixture of branched chain amino acids containing 3 amino acids associated with the urea cycle (Hep-OU) were infused to control subjects and patients with severe hepatic disease. Alterations in serum aminograms, blood ammonia levels and electroencephalograms following the infusion were studied and compared with those obtained by a commercially available amino acid mixture. Short-term or continuous infusion of a commercially available amino acid solution to cirrhotic patients caused an increase in methionine, phenylalanine and tyrosine and a decrease in branched chain amino acids. These post-infusion results were similar to the patterns seen in hepatic encephalopathy. In cirrhotic patients, infusion of Fischer solution which contains small quantities of methionine and phenylalanine produced an increase in the concentrations of these 2 amino acids, probably because of impaired utilization by the injured liver. No marked alterations in serum aminograms, however, were observed in cirrhotic patients either immediately after, or 3 h after, the end of the Hep-OU infusion. Reduction of methionine, tyrosine and phenylalanine levels and elevation of the molar ratio of (valine + leucine + isoleucine)/(phenylalanine + tyrosine) were significant. The infusion of Hep-OU to patients with liver cirrhosis or subacute hepatitis resulted in clinical and neurological improvements and the restoration of the molar ratio of branched chain amino acids/aromatic amino acids.

Key words: serum amino acids, hepatic encephalopathy, liver cirrhosis, fulminant and subacute hepatitis, aromatic and branched chain amino acids.

Hepatic failure is associated with considerable distortion in serum amino acid levels; the levels of tyrosine, phenylalanine and methionine in serum being elevated whereas those of branched chain amino acids are diminished (1). This pattern of amino acid imbalance is thought to be of considerable importance

to cerebral function in patients with hepatic disease (2). Munro *et al.* (3) suggested that entry of tryptophan into the brain might be regulated by the concentrations of other neutral amino acids competing for cerebral uptake, notably branched chain amino acids. The higher levels of insulin in the blood of patients with advanced cirrhosis of the liver would promote excessive removal of branched chain amino acids by muscle, leading to a reduction of the competitive action of branched chain amino acids on the entry of tryptophan into the brain (3). It is therefore of great importance to normalize the levels of branched chain amino acids in hepatic disease.

Patients with advanced cirrhosis of the liver are frequently limited to less than 40 g daily dietary protein or completely fasted because of the high ammonia levels in the blood or the upper gastrointestinal bleeding. The malnutrition in patient with cirrhosis is accompanied by a catabolic state with negative nitrogen balance. This results in hepatic encephalopathy probably through the increased formation of various amines and degraded metabolites of protein (4). These protein depletions are a major problem in the treatment of cirrhotic patients. The provision of adequate nutrition by mouth is made difficult by protein intolerance. Techniques for intravenous hyperalimentation with an adequate amino acid solution can safely provide large amounts of amino acids with positive nitrogen balance (5). The problem, however, is just what kinds of amino acid mixture are beneficial in the nutritional therapy of patients with advanced hepatic disease.

Our previous study indicated that elevated levels of serum aromatic amino acids could be significantly reduced with restoration of the normal molar ratio of (valine + leucine + isoleucine)/(phenylalanine + tyrosine) (abbreviated below to BCAA/AAA) by infusion of only 3 branched chain amino acids (1). We prepared a new mixture of branched chain amino acids containing glutamate, aspartate and ornithine (Hep-OU) for the present study. A commercially available amino acid solution and another amino acid mixture high in branched chain amino acids and low in aromatic amino acids (Fischer solution) (6) were also infused to patients with severe hepatic disease. The effect of each of the 3 types of amino acid mixture on serum aminograms, biochemical parameters in the blood and electroencephalograms was compared.

SUBJECTS AND METHODS

The subjects studied were 11 control subjects, 17 patients with non-malignant cirrhosis of the liver, 3 with fulminant hepatitis and 2 with subacute hepatitis. These patients had been admitted to the Okayama University, Saiseikai General and Kumayama Hospitals over a 3-year period. Diagnosis was based on liver biopsy and autopsy findings as well as the clinical picture in 3 cases of liver cirrhosis and

I of subacute hepatitis. The mean grade of encephalopathy and electroencephalographic findings was based on Sherlock's (7) and Parsons-Smith's (8) classifications, respectively. Quantitative determinations of serum amino acids were carried out by a Nihon-Denshi JCL-6AH amino acid analyzer as described previously (1). Blood ammonia was assayed according to the methods of Fujii and Okuda (9) and Seligson and Hirahata (10), and other biochemical analyses of blood were performed according to routine laboratory methods (1). Nitrogen balance was determined by the Kjeldahl method (11).

The three solutions of amino acid mixture in a volume of 500 ml are shown in Table 1. These solutions contain 100g glucose, which was added just before

TABLE 1. COMPOSITION OF AMINO ACID SOLUTIONS

Amino acids	Commercially available amino acids	Fischer solution	Hep-OU
		(g/500 ml)	
Leucine*	2.28	3.30	4.15
Valine*	1.38	2.50	3.05
Isoleucine*	1.19	2.70	2.75
Methionine*	0.87	0.30	
Cystine	0.05		
Phenylalanine*	1.95	0.30	
Tyrosine	0.11		
Tryptophan*	0.37	0.23	
Threonine*	1.01	1.35	
Lysine*	1.57	2.28	
Arginine	2.46	1.80	
Histidine	1.04	0.70	
Alanine	1.64	2.25	
Aspartic Acid	0.40		1.00
Glutamic acid	0.20		1.50
Glycine	3.14	2.70	
Proline	2.13	2.40	
Serine	0.93	1.50	
Cysteine		0.12	
Ornithine			0.50
Total	22.72	24.43	12.95

* Essential amino acids

the start of the infusion. The solutions were infused intravenously over a 3 h period (2.8 ml/min or 0.56 g glucose/min) early in the morning. Parenteral nutrition through a superior vena cava catheter was performed in patients with cirrhosis of the liver (Case N.F.) and subacute hepatitis (Case S.K.). Infusion to Case N.F. was maintained at 1.2 g of protein/kg body weight/day and at about 90 non-

protein Calories/g of nitrogen. Hep-OU or Fischer solution was infused daily with glucose to Case S.K. for only a 3 h period each morning. In the rest of the time, 20% glucose was given continuously with 0.3-0.5 g protein/kg body weight/day. The clinical details of these patients are described in the Results section.

RESULTS

Serum amino acid levels in patients with hepatic disease. Amino acid analyses of cirrhotic patients with and without hepatic encephalopathy consistently revealed elevated levels of aromatic amino acids and methionine, together with depressed values of 3 branched chain amino acids (Table 2). Methionine, tyrosine

TABLE 2. MEAN SERUM AMINO ACID LEVELS IN NORMAL SUBJECTS AND PATIENTS WITH HEPATIC DISEASE

Amino acid	Amino acid level (μ moles/l)				
	Normal subject (5)	Liver cirrhosis		Fulminant hepatitis (3)	Subacute hepatitis (2)
		With Encephalopathy (7)	Without (3)		
Valine	208 \pm 23	121 \pm 10	110 \pm 20	398 \pm 107	142
Leucine	128 \pm 13	69 \pm 11	45 \pm 8	270 \pm 111	74
Isoleucine	67 \pm 7	45 \pm 10	27 \pm 3	92 \pm 55	35
Methionine	30 \pm 6	165 \pm 58	59 \pm 14	413 \pm 121	318
Phenylalanine	68 \pm 6	129 \pm 16	107 \pm 16	554 \pm 181	164
Tyrosine	66 \pm 5	178 \pm 10	142 \pm 10	383 \pm 37	205
Tryptophan	87 \pm 5	106 \pm 6	106 \pm 10	329 \pm 69	89
Free tryptophan	6 \pm 1	14 \pm 2	7 \pm 1	31 \pm 6	—
BCAA/AAA	3.0 \pm 0.3	0.8 \pm 0.1	0.8 \pm 0.2	0.8 \pm 0.1	0.8

() ; No. of cases studied

and phenylalanine rose to a smaller extent in non-encephalopathic cirrhosis than in encephalopathic cirrhosis. Other essential and nonessential amino acids were either normal or only minimally changed. All amino acids were markedly elevated in patients with fulminant hepatitis, the results being greatly different from those of cirrhotic patients. Two patients with subacute hepatitis showed a similar pattern of serum amino acids to that found in fulminant hepatitis except for decreased levels of the 3 branched chain amino acids. Elevated levels of free tryptophan were observed in hepatic encephalopathic patients, but diminished molar ratios of BCAA/AAA were found in most patients with hepatic disease. No apparent correlation between free tryptophan levels and this molar ratio was observed in encephalopathic patients. Markedly and mildly increased amounts of 8 essential and 14 nonessential amino acids in serum were observed in patients

with fulminant and subacute hepatitis but patients with cirrhosis and encephalopathy showed minimally elevated levels of nonessential amino acids.

Infusion of a commercially available synthetic amino acid mixture to cirrhotic patients. After infusion of a commercially available amino acid solution to a cirrhotic patient, marked decreases in branched chain amino acids and elevations of methionine, phenylalanine and tyrosine occurred 3 h after the end of a 3 h-infusion, indicating that the commercially available amino acid mixture not only failed to correct serum amino acid imbalance but also induced aminograms similar to those obtained in hepatic encephalopathy (Fig. 1). The continuous infusion of a commercially available amino acid solution to Case N.F. was carried out under the conditions described in Subjects and Methods (Fig. 2). Case N.F., a

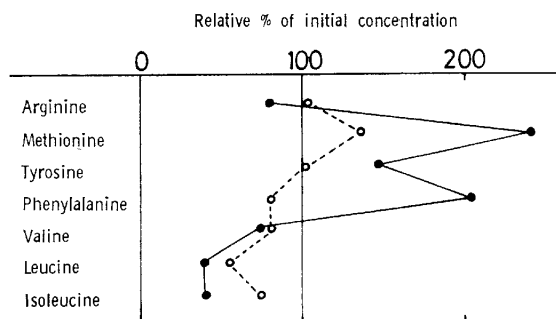


Fig. 1. Effect of infusion of a commercially available amino acid mixture on serum amino acid levels in a control subject and a patient with liver cirrhosis. Infusion of a commercially available amino acid solution containing 100 g glucose/500 ml was performed during 3 h to a normal subject (26-year-old male, ○··○), as described under Subjects and Methods, and a patient with histologically proven cirrhosis (●—●, 54-year-old male) who was well compensated with a normal level of blood ammonia. The blood for analysis of serum amino acid levels was drawn 3 h after the end of infusion.

61-year-old male, was admitted on March 4 because of abdominal distension and hematemesis. He was given a blood transfusion immediately. Endoscopic examination indicated esophageal varices and gastric ulcers. The level of alpha-fetoprotein (AFP) was higher than 1280 ng/ml, but hepatoma could not be confirmed by liver scintigram, angiography or Pap smears of ascites cells. He was diagnosed clinically as decompensated cirrhosis of the liver. Bleeding from the upper gastrointestinal tract continued intermittently from May 20. There was no good urinary response to furosemide, and ascites increased gradually. This was tapped frequently. His therapy consisted of nothing by mouth and total parenteral nutrition using a commercially available amino acid-dextrose mixture from June 11 to 18. Methionine and phenylalanine levels increased, branched chain amino acids remained unchanged, and the molar ratio of BCAA/

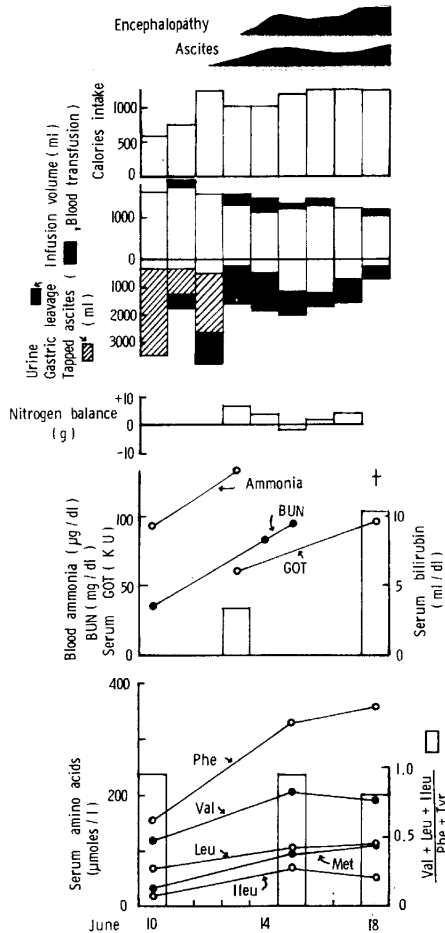


Fig. 2. Clinical course in a patient with cirrhosis of the liver (Case N.F.) undergoing long-term infusion of a commercially available amino acid mixture.

AAA decreased. The nitrogen balance became positive from the 2nd day of parenteral nutrition. Bleeding continued and his level of consciousness gradually decreased. This was accompanied by abnormal electroencephalographic findings and he died on June 18.

Effect of Fischer solution on serum amino acid levels in a control subject and a cirrhotic patient. Amino acids increased immediately after the end of a 3 h-infusion of the Fischer solution to a control subject were threonine, proline, glycine, alanine, ornithine, lysine, histidine, arginine and the 3 branched chain amino acids (Fig. 3). Serum aminograms reflected the composition of the amino acid solution infused. However, aspartate, glutamate, methionine, phenylalanine

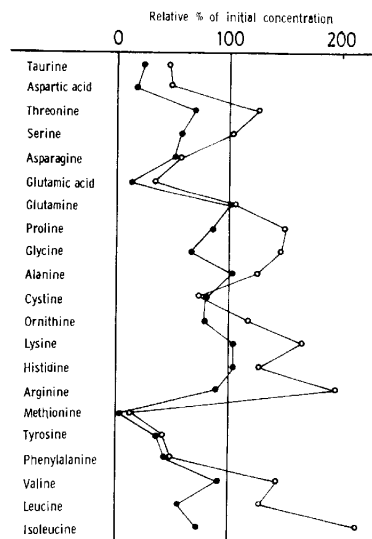


Fig 3

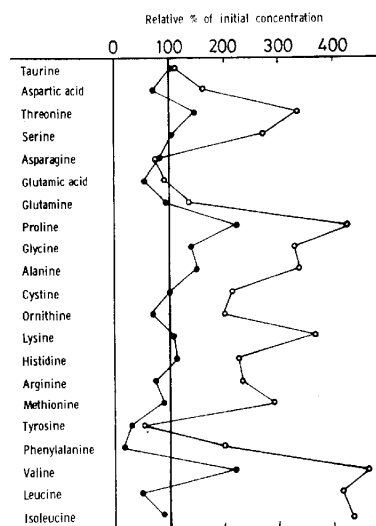


Fig 4

Fig. 3. Effect of infusion of Fischer solution on serum amino acid levels in a control subject. Infusion of Fischer solution with 100 g glucose was similarly carried out for a healthy 63-year-old man. Amino acid analyses were performed immediately ($\circ-\circ$) and 3 h ($\bullet-\bullet$) after the end of 3 h-infusion, in the same way as for Figs. 4-6.

Fig. 4. Effect of infusion of Fischer solution on serum amino acid levels in a patient with cirrhosis of the liver. A 59-year-old housewife with cirrhosis of the liver who was kept on a protein-restricted diet (about 30 g/day) for a long time because of blood ammonia levels of 150-200 $\mu\text{g}/\text{dl}$. Diagnosed by liver biopsy 2.5 years ago as chronic hepatic coma according to Sherlock's classification (7). Hepatic encephalopathy occurred at a frequency of 2 or 3 times a year, but consciousness was clear at the time of infusion.

and tyrosine levels were all markedly decreased both immediately after, and 3 h after, the end of infusion. Branched chain amino acids also showed lower levels at 3 h after infusion. In one case of liver cirrhosis with chronic encephalopathy (7), strikingly elevated serum levels of the amino acids in the amino acid solution given were observed immediately after the end of the infusion (Fig. 4). Many amino acids including methionine, tyrosine and phenylalanine tended to decrease 3 h after the end of infusion. When the solution contained even small quantities of methionine and phenylalanine, their levels rose temporarily but markedly to 200-300% of the initial levels immediately after the end of infusion. Methionine levels has only fallen slightly even 3 h after the end of the infusion. This is a marked difference from the results for the control subjects.

Effect of Hep-OU on serum amino acid levels in a control subject and a cirrhotic patient. Our previous report has shown that amino acids decreased after infusion

of 3 branched chain amino acids were members associated with the urea cycle, particularly aspartate, glutamate and ornithine (1). Small quantities of these 3

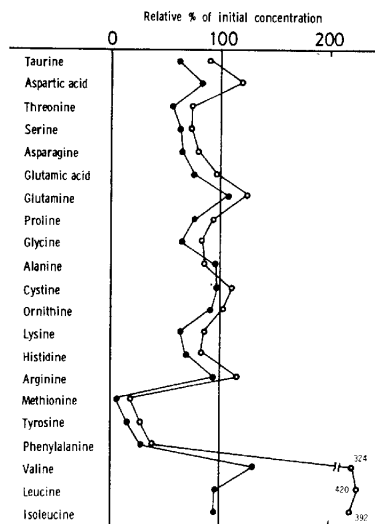


Fig. 5

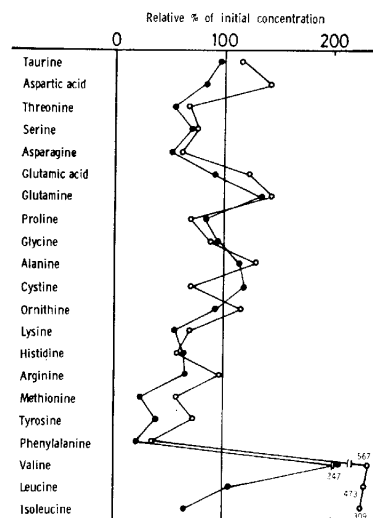


Fig. 6

Fig. 5. Effect of Hep-OU infusion on serum aminograms in a control subject. Infusion of Hep-OU with 100 g glucose was similarly performed in the same way for a control subject, a 58-year-old housewife.

Fig. 6. Effect of Hep-OU infusion on serum amino acid levels in a patient with cirrhosis of the liver. A 45-year-old man with cirrhosis who was well compensated and took a daily protein intake of 70 g. Blood ammonia levels were 90–120 $\mu\text{g}/\text{dl}$. Diagnosed on clinical findings.

amino acids were added to prepare Hep-OU solution. Serum aminograms both immediately after, and 3 h after, the end of a Hep-OU infusion were better than those after infusion of the previously prepared solution of 3 branched chain amino acids alone; that is the reduction of aspartate, glutamate and ornithine was prevented. Moreover, tyrosine, methionine and phenylalanine diminished similarly to 5–40% of the initial value (Fig. 5). Amino acid levels in a patient with cirrhosis of the liver were mildly depressed or elevated following Hep-OU infusion except that marked elevations of branched chain amino acids and greatly diminished levels of methionine and phenylalanine were observed immediately after, and 3 h after, the infusion, respectively (Fig. 6). Marked fluctuations in other amino acid levels after Hep-OU infusion were not observed in a cirrhotic patient. Diminished levels of methionine, tyrosine and phenylalanine were similar to those obtained with Fischer solution. The blood ammonia level fell slightly and the previously elevated levels of serum nonesterified fatty acids

(NEFA) returned to normal values after infusion of this solution. A marked response of insulin to the administration of amino acid-glucose mixture occurred in one patient with cirrhosis. Changes in the molar ratio of BCAA/AAA after the infusion of different types of amino acid solutions are summarized in Fig. 7. Diminished ratios in patients with liver cirrhosis returned to control values and remained within normal limits for at least 6 h after the start of Hep-OU or Fischer solution. These results are different from those obtained by infusion of a commercially available amino acid mixture.

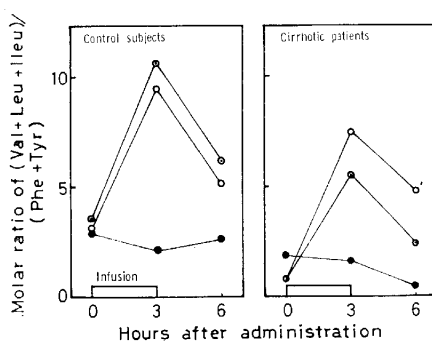


Fig. 7. Change in the molar ratio of BCAA/AAA following infusion of a solution of 3 types of amino acid mixture. A commercially available amino acid solution, ●; Fischer solution, ○ and Hep-OU, ◐.

Clinical and neurological improvements following infusion of Hep-OU and Fischer solution to patients with subacute hepatitis and liver cirrhosis. Case S.K., a 51-year-old housewife, was admitted on June 28 complaining of anorexia and deep jaundice of a week's duration. She had had previous episodes of jaundice with marked elevation of serum transaminase activities for 20 days from the end of February to March and again for 10 days in April. Prednisolone had been administered almost continuously from the end of February. Serum bilirubin rose gradually to 27 mg/dl and GPT activities varied from 780 to 1090 during the first 3 weeks after admission. Even with the introduction of steroid therapy from the 3rd week, there was no prompt improvement in serum bilirubin levels. Total parenteral nutrition with about 1500 Calories/day was started from June 20. The serum bilirubin rose to 40 mg/dl and disseminated intravascular coagulation developed. She died on July 26 despite the administration of large quantities of heparin. Her consciousness remained relatively clear till death, although electroencephalographic findings showed severe cerebral dysfunction. Serum aminograms and electroencephalographic findings after infusion of Hep-OU (July 20) or Fischer solution (July 21) are shown in Table 3 and Fig. 8. The

changes in serum levels of several amino acids with time are also shown (Table 3). Further abnormal aminograms were found immediately after infusion of Fischer solution and seem to be related to the amino acid composition of the solution infused. Decreases in methionine, tyrosine and phenylalanine after infusion of either solution were again small in this case as compared with those in cirrhotic patients. Levels of the 3 branched chain amino acids rose, then fell and

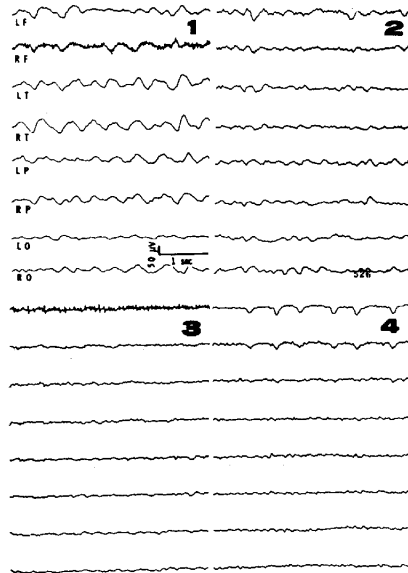


Fig. 8. Change in electroencephalographic findings in a patient with cirrhosis of the liver (Case U.K.) following Hep-OU infusion. Electroencephalographic findings before and after Hep-OU are illustrated. 1, Before; 2, immediately after; 3, 3 h following the end of Hep-OU (December 23); and 4, the morning of December 24.

TABLE 3. CHANGES OF SERUM AMINO ACID LEVELS IN A PATIENT WITH SUBACUTE HEPATITIS AFTER INFUSION OF HEP-OU AND FISCHER SOLUTION

Solution	Time after the start of infusion (Hour)	Amino acid level (μ moles/l)						BCAA/AAA
		Valine	Leucine	Isoleucine	Methionine	Tyrosine	Phenylalanine	
Hep-OU (July 20)								
	0	106	76	54	508	228	140	0.6
	3	351	316	158	478	162	78	3.4
	6	116	46	26	439	144	61	0.9
Fischer (July 21)								
	0	46	22	27	429	178	79	0.4
	3	366	196	189	524	151	93	3.1
	6	146	56	39	475	159	110	1.0

continued to decrease below the initial levels till the next morning. Continuous administration during 24 h of branched chain amino acids would be necessary to maintain these amino acids within normal ranges. Two to three c/s of basic activities with triphasic waves (Grade E) were continuously observed before infusion of Hep-OU on July 20. The basic activities became 5-6 c/s immediately after, and 4-5 c/s (Grade D) 3 h after, the end of the infusion. Some slow α waves appeared (Grade C) immediately after the end of Fischer solution and θ waves reappeared thereafter.

Case U.K., a 63-year-old male, entered the hospital on May 30 because of drowsiness. He was diagnosed as hepatic encephalopathy from clinical and laboratory findings 4 years earlier. Encephalopathic episodes (mostly Grade 2) had occurred 2-6 times in a year without any specific cause. These usually recovered gradually over a period of 3-6 days. Elevated levels of blood ammonia are at present considered unrelated to the occurrence of hepatic encephalopathy. He became drowsy on October 8 and suddenly lapsed into deep coma on October 9. L-DOPA, steroid hormones and arginine-glutamate mixture were injected but proved ineffective. Two h after the commencement of an infusion of Hep-OU (500 ml of 10% glucose) on the morning of October 10, the patient awakened from the hepatic encephalopathy. Consciousness was completely normal by the end of a 3 h-infusion. The aminogram 2.5 h after the end of the 2nd infusion of Hep-OU was compared with that at the time of hepatic encephalopathy (Grade 4) on November 3. Levels of phenylalanine, tyrosine and branched chain amino acids as well as the molar ratio of BCAA/AAA were well within normal limits but the methionine level was very low after the Hep-OU infusion on October 10. The serum aminogram on November 3 indicated a molar ratio of 0.5 with extremely low levels of branched chain amino acids and slightly elevated levels of

TABLE 4. CHANGES OF SERUM AMINO ACID LEVELS IN A PATIENT WITH LIVER CIRRHOSIS AFTER INFUSION OF HEP-OU

Amino acid	Amino acid level (μ moles/l)			
	October 10	November 3		November 4
		Before Hep-OU	3 Hours after the end of Hep-OU	
Valine	225	42	253	116
Leucine	107	14	84	42
Isoleucine	64	15	61	33
Methionine	0.2	17	8	20
Tyrosine	70	86	55	60
Phenylalanine	59	67	45	57
BCAA/AAA	3.1	0.5	4.0	1.6

tyrosine. Encephalopathy again improved rapidly by Hep-OU infusion alone, the ratio being 4.0 3 h after the end of the infusion. In the encephalogram, a slower basic activity was found than before the Hep-OU infusion on December 23 (Fig. 8). Electroencephalograms changed to a basic activity of 5–6 c/s slow α waves immediately after, and 3 h after, the end of the infusion. The improvement was still present the next morning.

DISCUSSION

Patients with advanced liver disease frequently develop severe malnutrition and marked imbalance of serum amino acids. So far, there has been little success in correcting these abnormalities of amino acid levels, which are thought to be related to poor utilization or rapid turnover of amino acids and to the negative nitrogen balance of the catabolic state (12). Administration of a commercially available mixture of nonessential and essential amino acids to cirrhotics resulted in a strikingly abnormal serum amino acid pattern with a lowered molar ratio of BCAA/AAA. Continuous infusion of a commercially available amino acid mixture to Case N.F. in amounts equivalent to 72 g of protein every 24 h also resulted in elevated levels of aromatic amino acids without restoration of branched chain amino acid levels. This picture has been associated with the onset of hepatic encephalopathy. The levels of neurotransmitters mediating central nervous system function may be controlled by serum amino acids, particularly neutral amino acids (2). If abnormal amino acid patterns are related to hepatic encephalopathy, normalization of serum amino acid imbalance would be of prime importance and beneficial in the treatment of neurological abnormalities.

In fact, preliminary results in patients with hepatic encephalopathy of various etiologies have already suggested that parenteral nutrition using a solution of amino acid mixture high in branched chain amino acids and low in aromatic amino acids apparently improve central nervous system function (13). Our previous results indicated that infusion of only 3 branched chain amino acids was effective in reducing aromatic amino acid levels but that it caused a decrease in amino acids associated with the urea cycle. Based on these results, glutamate, aspartate and ornithine were added in small amounts to the previous solution of 3 branched chain amino acids in order to prevent the striking reduction of these amino acids. This solution apparently caused decreased levels of methionine, tyrosine and phenylalanine in a control subject and in patients with liver cirrhosis or subacute hepatitis. However, a marked elevation in many amino acids as well as methionine and phenylalanine was markedly elevated immediately after infusion of Fischer solution to patients with cirrhosis of the liver and subacute hepatitis. Therefore, Hep-OU may be safe and useful in the treatment of hepatic encephalopathy. This solution alone should not be used for a long period

because its composition of amino acids is not nutritionally adequate. Parenteral nutritional supplement with a specially designed amino acid mixture should be started as early as possible in the presence of diminishing oral dietary intake. Otherwise the catabolic state of the cirrhotic patient may precipitate upper gastrointestinal bleeding, infection and electrolyte imbalance, easily bringing about hepatic encephalopathy. The total amounts of amino acid to be administered should be decided by measuring daily nitrogen balance.

A clinical problem frequently encountered is that the nutrient infusion volume has to be greatly restricted because of oliguria in advanced cirrhosis. Autogeneous and concentrated ascitic fluid may have to be reused by mixing large amounts of glucose and amino acids in cirrhotic patients with intractable ascites or hepatorenal syndrome. Commercially available mixtures of essential and nonessential amino acids were not tolerated in advanced cirrhotic patients, even in amounts of up to 20 g/day. However, administration of a modified solution up to 100 g protein equivalents every 24 h is possible and has even been associated with improvements in hepatic function (14). The technique of parenteral nutrition can be widely applied in patients with advanced cirrhosis of the liver and studies of this technique should clarify the pathophysiology of hepatic encephalopathy.

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