*Acta Medica Okayama*

*Volume* 48, *Issue* 1 1994 *Article* 5

FEBRUARY 1994

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## Abstract

We administered a branched-chain amino acid (BCAA) infusion to 16 patients with hepatic failure and two healthy subjects, and then evaluated its effects on ammonia metabolism and amino acid metabolic pool. Immediately after the BCAA infusion, the venous blood ammonia concentration increased in 12 of 15 patients with hepatic failure and in both two healthy subjects. Glutamine (Gln) also rose in all cases following the BCAA infusion, and this rise was particularly marked in the hepatic failure group. The increase in Gln due to the BCAA infusion and the arteriovenous difference in the pre-administration ammonia concentration showed a good correlation. These results suggest an increase in glutamine cycle capacity in patients with hepatic failure.

**KEYWORDS:** branched-chain amino acide, hepatic failure, ammonia, glutamine cycle

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*PMID: 8191913 [PubMed - indexed for MEDLINE]

ACTA MED OKAYAMA 1994; 48(1): 25-30

# Administration of a Branched-Chain Amino Acid Preparation during Hepatic Failure: A Study Emphasizing Ammonia Metabolism

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We administered a branched-chain amino acid (BCAA) infusion to 16 patients with hepatic failure and two healthy subjects, and then evaluated its effects on ammonia metabolism and amino acid metabolic pool. Immediately after the BCAA infusion, the venous blood ammonia concentration increased in 12 of 15 patients with hepatic failure and in both two healthy subjects. Glutamine (Gln) also rose in all cases following the BCAA infusion, and this rise was particularly marked in the hepatic failure group. The increase in Gln due to the BCAA infusion and the arteriovenous difference in the pre-administration ammonia concentration showed a good correlation. These results suggest an increase in glutamine cycle capacity in patients with hepatic failure.

**Key words:** branched-chain amino acids, hepatic failure, ammonia, glutamine cycle

There have been many reports (1-4) describing the usefulness of branched-chain amino acid (BCAA) preparations in treating hepatic encephalopathy. Some cases exhibit a rise in blood ammonia levels immediately after intravenous administration of BCAA preparations, however, it is thought that its effect on the amino acid metabolic pool differs depending on the individual's pathological condition.

The negative effects of its administration must be taken into consideration from the fact that its administration means the administration of a source of nitrogen. Therefore, with the purpose of clarifying the response to the administration of a BCAA preparation in patients with chronic hepatic failure, we evaluated the ammonia processing capacity of this drug. The data obtained in evaluating the ammonia and amino acid metabolic pool were interesting and are therefore reported here.

## Subjects and Methods

The subjects of this study were 16 patients with hepatic failure who were treated at the First Department of Internal Medicine of Okayama University Medical School. The patients had displayed symptoms of hepatic encephalopathy during the month prior to selection, and were judged by the primary attending physician as able to begin a course of Aminoleban administration. Two healthy subjects were also included in this study. Informed consent was obtained from these subjects. Evaluation of the cause of the hepatic failure showed 11 cases with cirrhosis of the liver (three cases were complicated by liver cancer, and one case had chronic renal failure), two cases of idiopathic portal hypertension, and one case each of primary biliary cirrhosis, acute on chronic hepatitis, and of portal systemic shunt (Table 1).

The method of administration was as follows. A dose of 500 ml of Aminoleban, a BCAA preparation (Otsuka Pharmaceuticals, Tokyo, Japan) was administered in the early morning before meals by drip infusion over 3 h. The composition of this drug is shown in Table 2.

The following items were determined: Ammonia concentrations in the arterial/venous blood and urine immediately before beginning and immediately after completing Aminoleban administration, plasma free amino acid concentrations in the venous blood, arterial blood gas, and urea nitrogen in the venous blood and urine. General hepatic function tests were performed before the administration. Arterial blood was drawn from the femoral artery and venous blood was drawn from the antecubital vein. Determinations were done as follows. Arterial and venous blood ammonia concentrations were determined by the micro-dispersion method (Amitest-N, Chugai Pharmaceu-

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**Table 1** Patients with hepatic failure followed by an episode of hepatic encephalopathy

| No. | Age | Sex | Diagnosis | Bil. (mg/dl) | Alb. (mg/dl) | GOT (IU/l) | CHE (IU/l) | T. Cho (mg/dl) | K-ICG | Fischer ratio |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 52 | F | LC | 8.76 | 3.66 | 66 | 44 | 144 | - | 0.83 |
| 2 | 52 | M | LC | 2.23 | 2.99 | 75 | 41 | 155 | 0.04 | 0.83 |
| 3 | 40 | M | LC | 4.16 | 3.11 | 60 | 28 | 58 | 0.04 | 0.85 |
| 4 | 47 | M | LC | 9.82 | 3.01 | 69 | 30 | 63 | 0.03 | 0.94 |
| 5 | 38 | M | LC | 2.27 | 3.31 | 59 | 47 | 142 | 0.07 | 0.95 |
| 6 | 44 | M | LC | 47.87 | 3.04 | 83 | 45 | 45 | - | 1.14 |
| 7 | 54 | M | LC | 9.04 | 3.24 | 60 | 31 | 50 | 0.04 | 1.29 |
| 8 | 53 | F | LC, CRF | 0.7 | - | 32 | - | 139 | - | 1.38 |
| 9 | 70 | F | LC, HCC | 0.94 | 3.36 | 90 | 63 | 144 | 0.05 | 1.02 |
| 10 | 60 | M | LC, HCC | 2.23 | 3.06 | 55 | 21 | 68 | 0.03 | 1.22 |
| 11 | 68 | M | LC, HCC | 2.13 | 2.97 | 46 | 63 | 99 | 0.04 | 2.35 |
| 12 | 51 | F | IPH | 0.43 | 3.55 | 41 | 71 | 145 | 0.06 | 1.23 |
| 13 | 57 | F | IPH | 1.09 | 3.39 | 50 | 95 | 138 | 0.06 | 1.47 |
| 14 | 46 | F | PBC | 1.14 | 3.91 | 142 | 101 | 233 | 0.07 | 1.81 |
| 15 | 39 | M | Acute on chronic | 12.74 | 3.85 | 95 | 82 | 137 | 0.05 | 1.02 |
| 16 | 58 | M | P-S shunt | 1.16 | 3.03 | 52 | 79 | 133 | 0.13 | 1.75 |

Bil.: bilirubin; Alb.: albumin; GOT: glutamic oxaloacetic transaminase; CHE: cholinesterase; T. Cho.: total cholesterol; LC: liver cirrhosis; CRF: chronic renal failure; HCC: hepatocellular carcinoma; IPH: idiopathic portal hypertension; PBC: primary biliary cirrhosis; p-s shunt: portal-systemic shunt

**Table 2** Composition of the synthetic amino acid solution (Aminoleban) used in this stuby

| Amino acids | Contents (g/500 ml) |
|---|---|
| L-Isoleucine | 4.50 |
| L-Leucine | 5.50 |
| L-Lysine | 3.04 |
| L-Methionine | 0.50 |
| L-Phenylalanine | 0.50 |
| L-Threonine | 2.25 |
| L-Tryptophan | 0.35 |
| L-Valine | 4.20 |
| L-Cysteine | 0.14 |
| L-Arginine | 3.00 |
| L-Histidine | 1.20 |
| L-Alanine | 3.75 |
| Glycine | 4.50 |
| L-Proline | 4.00 |
| L-Serine | 2.50 |
| Total amino acids | 39.93 |

ticals, Tokyo, Japan), and urinary ammonia concentrations were determined by an enzymatic method (Detaminer $NH_3$, Kyowa Hakko, Tokyo, Japan). Plasma free amino acid analysis was performed using a Hitachi Model 835 automatic Amino Acid Analyzer. Arterial blood gas analysis was done using a completely automatic blood gas electrolyte analyzer (ABL-4, Shinko Koeki, Tokyo, Japan). Urea nitrogen and general hepatic function tests were performed using Hitachi automatic analyzers (No.736, No.7150).

Statistical methods employed were simple regression analysis and Student's $t$ test. $P$ values of 0.01 or less were considered as statistically significant.

## Results

***Changes in ammonia, urea nitrogen and blood gases due to administration of Aminoleban.*** Although the arterial blood ammonia concentration declined in two cases (cases 8 and 10), it rose in all other cases, including the two healthy subjects. Venous blood ammonia concentrations declined in three cases (cases 6–8), but rose in all other cases, including the two healthy subjects.

The patients indicating positive decrease of blood ammonia concentrations, showed no uniform tendency from the point of their background except for pateints with hyperammonemia (Table 1).

Blood urea nitrogen (BUN) rose in all cases but one

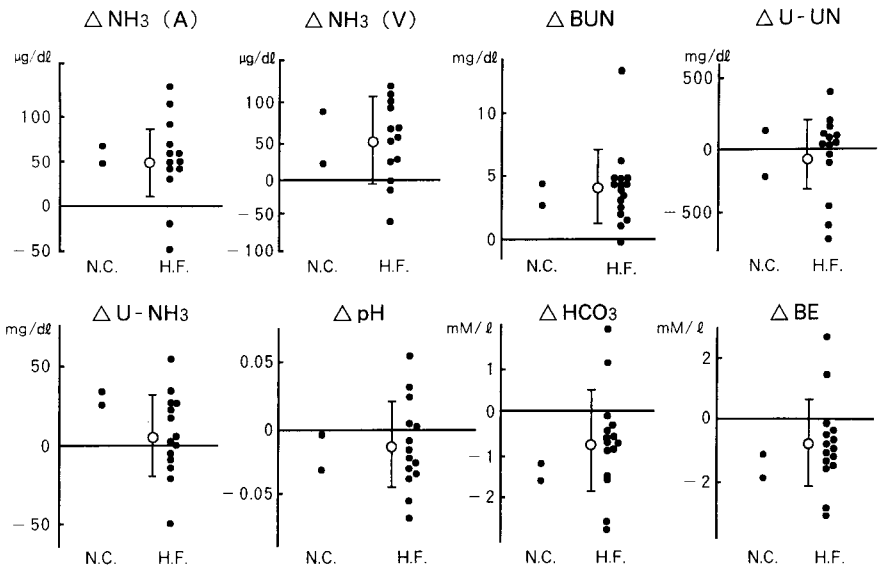


**Fig. 1** Changes in ammonia concentration in arterial (A) and venous (V) blood and urine (U), urea nitrogen (UN) in venous blood and urine, arterial pH, $HCO_3^-$ and base excess (BE) upon infusion of a preparation rich in branched-chain amino acids (BCAA infusion). Open circles and bars indicate mean ± SD of hepatic failure group. (NC: normal control, HF: hepatic failure)

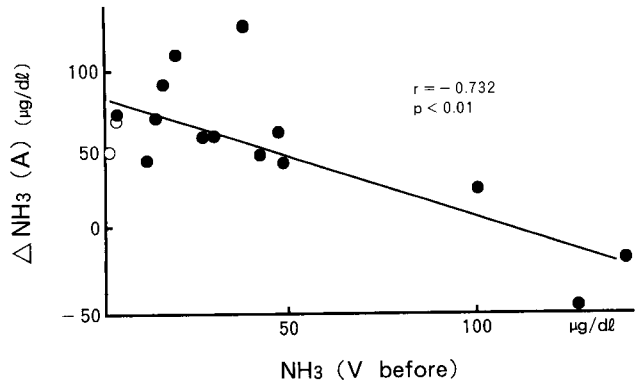


**Fig. 2** The correlation between venous blood ammonia concentration before branched-chain amino acid (BCAA) infusion and the change in arterial blood ammonia concentration before and after infusion (●: hepatic failure, ○: normal control). The correlation coefficient was −0.732 ($p < 0.01$), thus indicating a negative correlation.

in which there was almost no change. A rise in urinary urea nitrogen was therefore anticipated, but urinary urea nitrogen and urinary ammonia concentrations displayed no uniform tendency due to a dilution effect of the urine.

Although blood pH displayed slight changes within a ± 0.05 range, no uniform tendency was observed. However, $HCO_3^-$ and base excess were observed to decline in all but two cases. They also declined in both healthy subjects (Fig. 1).

***Changes in the ammonia concentration in arterial and venous blood.*** The change in the arterial blood ammonia concentration before and after the administration of Aminoleban and its relationship to the venous blood ammonia concentration before administration exhibited a correlation coefficient of $-0.732$ ($p < 0.01$) as shown in Fig. 2, thus indicating a negative correlation. The administration of the BCAA infusion tended to elevate the ammonia concentration in cases with low venous blood ammonia concentrations. The correlation coefficient between the arteriovenous difference in the blood ammonia concentrations before administration and the arterial blood ammonia concentration was 0.547 ($p < 0.05$) (Fig. 3). Although a correlative tendency cannot be denied, it was hardly significant. However, except for the patients with over 100 μg/dl in arterial blood ammonia concentration before administration, the correlative coefficient was 0.754 ($p < 0.01$), indicating a good corre-

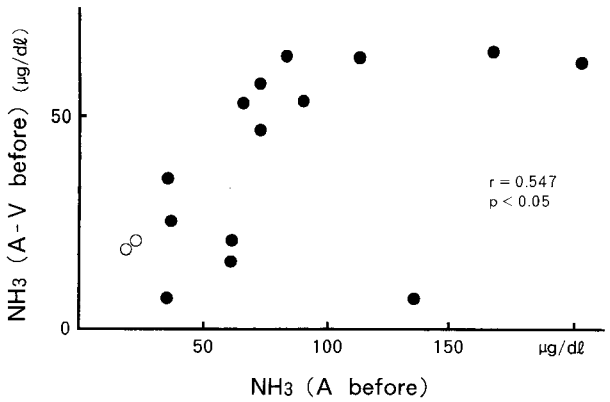


**Fig. 3** The correlation between the arteriovenous difference in the blood ammonia concentration (A-V before) and the arterial blood ammonia concentration (A before) before branched-chain amino acid (BCAA) infusion. The correlation coefficient was 0.547 ($p < 0.05$), so a significant correlation was not indicated. However, except for the patients with high arterial blood ammonia concentration (over 100 $\mu$g/dl) before administration, the correlative coefficient was 0.754 ($p < 0.01$), indicating a good correlation.

lation.

***Changes in glutamine (Gln) and alanine (Ala), and the ammonia arteriovenous difference.*** Gln and Ala are amino acids directly involved in BCAA metabolism. Gln was found to rise in all cases following administration of Aminoleban, and this rise was more marked in the hepatic failure group than in the healthy group. Ala is also contained in Aminoleban, and its administration resulted in a rise of Ala in all cases, but this increase was most marked in the hepatic failure group (Fig. 4).

The changes in Gln and Ala levels were correlated with ammonia processing capacity in skeletal muscle. The correlative coefficient between the arteriovenous difference in ammonia concentration before administration of Aminoleban and the increase in Gln was 0.734 ($p < 0.01$), indicating a good correlation (Fig. 5a).

No correlation was observed between the arteriovenous ammonia difference before administration of Aminoleban and the increase in Ala (Fig. 5b) ($r = 0.411$, $p < 0.2$).

## Discussion

An imbalance in plasma free amino acids is thought to be important as a mechanism of hepatic encephalopathy characterized by elevated aromatic amino acids and declined branched-chain amino acids (5–9). Fischer *et al.* (1) reported that hepatic encephalopathy can be improved by compensating for this amino acid imbalance. Based on the report of Fischer *et al.*, a specially combined preparation of amino acids, BCAA infusion, has come into wide use. However, although some cases show dramatic clinical improvement, other cases show no improvement, or even aggravation. In fact, although there have been reports (2–4) supporting its benefits, other reports have described no effects (10–13).

In this study, the ammonia concentration rose in most of the patients, and clearly rose in the two healthy

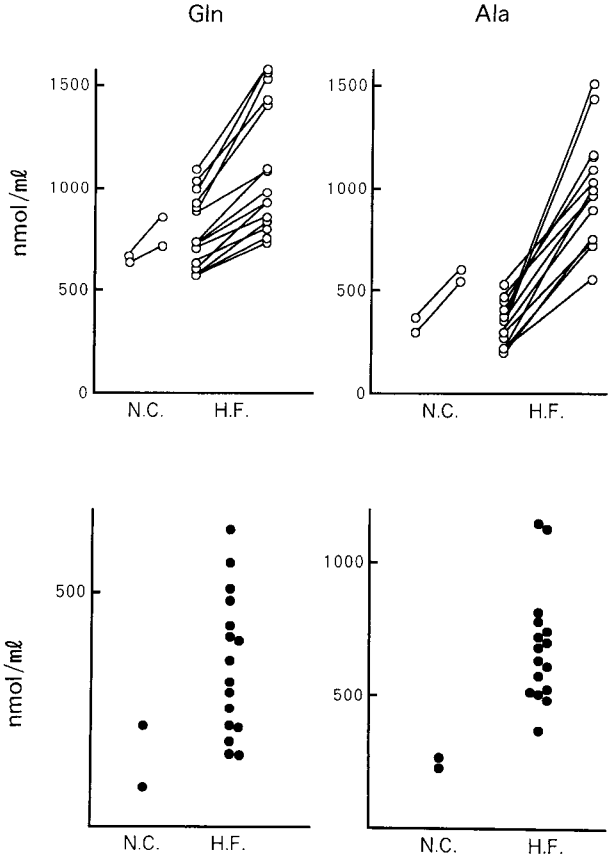


**Fig. 4** Changes in glutamine (Gln) and alanine (Ala) upon branched-chain amino acid (BCAA) infusion. The upper panel shows the changes in each ease, and the lower panel shows the increased value (NC: normal control, HF: hepatic failure). Gln and Ala were found to rise in all cases following BCAA infusion, and this rise was more marked in the hepatic failure group.

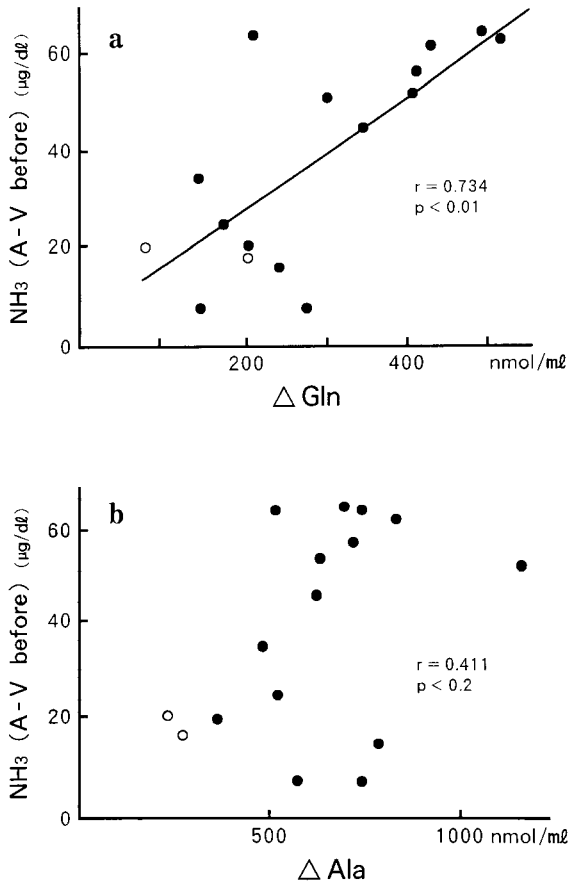


**Fig. 5** The correlation between the arteriovenous difference in the blood ammonia concentration before the administration of branched-chain amino acid (BCAA) preparation (A-V before) and the increase in glutamine (Gln) (**a**) and alanine (Ala) (**b**) following the administration (●: hepatic failure, ○: normal control). The correlative coefficient between the arteriovenous difference in ammonia concentration before BCAA infusion and the increase in glutamine was 0.734 ($p < 0.01$), indicating a good correlation. However, no correlation was observed between the arteriovenous ammonia difference before administration and the increase in Ala ($r = 0.411$, $p < 0.2$). A-V before: See Fig. 3.

subjects after BCAA preparation or Aminoleban was administered. This fact suggests that administration of the BCAA preparation can at least bring about an immediate rise in the ammonia concentration. Harper *et al.* (14) reported that intravenous administration of glycine brought about a rise in the ammonia concentration in fasting dogs. Kato *et al.* (15) reported that L-lysine brought about a rise in the ammonia concentration by blocking ornithine carbamyl transferase activity and by blocking ornithine uptake by the mitochondria. It will be necessary to study the composition of the amino acids other than BCAA included in BCAA preparations in the future.

The BCAA preparation serves two purposes in treating severe hepatic disorders. It is used to rectify amino acid imbalance, and to alleviate hepatic failure by functional compensation by the extra-hepatic organs that are relatively undamaged (16). A rise in ammonia clearance in the extra-hepatic organs has been identified in patients with hepatic failure (17, 18), but few reports have described studies in which BCAA was administered in such cases. Using $^{15}N$-leucine and $^{15}NH_4Cl$ in animal experiments under hepatic failure conditions, we have shown an increase in the glutamine cycle capacity in addition to the decline in urea cycle capacity (19, 20). The fact that the change in Gln and the pretreatment ammonia levels (arterial, arteriovenous difference) showed a good correlation in this study supports those results.

A significant correlation was not indicated between the arteriovenous difference in the blood ammonia concentrations before administration and the arterial blood ammonia concentration. However, when the patients with a high concentration of arterial blood ammonia (more than 100 $\mu$g/dl) were excluded, a significant correlation between them was observed ($r = 0.754$, $p < 0.01$). Therefore, we found it difficult to observe the ammonia processing capacity of the skeletal muscles reflected in the arteriovenous difference based on the single point index of arterial blood ammonia concentration, especially in the patients indicating high concentration of arterial blood ammonia.

The marked increase in Ala in the hepatic failure group was thought to be due to a reduction in the processing capacity of Ala in the liver. The increase in Ala was not attributed to production based on BCAA metabolism, because no correlation was observed between the changes in arteriovenous ammonia levels in Ala.

During our series of studies using $^{15}N$-leucine and $^{15}NH_4Cl$, we found that when the urea cycle capacity is reduced during hepatic failure, the glutamine cycle compensates to function at its maximum level. Because the synthesized Gln and ammonia are not rapidly processed by the urea cycle when BCAA is added, blood ammonia levels rise which suggests the possibility of further aggravation of the hepatic failure (20). In this study, however, it was thought that the marked increase in Gln and Ala in

the severe hepatic failure cases reflected "nitrogen" which was not being processed by the urea cycle.

Acknowledgments This work was supported by a grant from the Intractable Hepatitis Research Committee of the Japanese Ministry of Health and Welfare.

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Received February 18, 1993; Accepted june 7, 1993.