Use of branched chain amino acids for treating hepatic encephalopathy: clinical experiences

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SUMMARY The efficacy of branched chain amino acids in two consecutive clinical studies in patients with severe hepatic encephalopathy was tested. In the preliminary uncontrolled study 19 patients with grade 3-4 hepatic encephalopathy were given an intravenous solution containing leucine 11 g/l, isoleucine 9 g/l, and valine 8.4 g/l in 20% dextrose. A complete recovery of mental state was obtained in all patients in a mean time of 20.5 hours. In a subsequent controlled study 40 patients with grade 3-4 hepatic encephalopathy were randomly assigned to receive intravenous branched chain amino acid in 20% dextrose (group A) or oral lactulose (group B). Twelve patients (70.6%) in group A and eight (47%) in group B regained consciousness in a mean time of 27.6 and 31.5 hours, respectively. The difference in the recovery rate between the two groups, although evident, was not significant. Intravenous branched chain amino acids are thus at least as effective as lactulose in reversing hepatic coma.

These data argue strongly in favour of a therapeutic effect of branched chain amino acids in the treatment of hepatic encephalopathy in patients with chronic liver failure.

The characteristic plasma amino acid pattern, with high aromatic and low branched chain amino acids observed in chronic liver failure, is thought to have a causal role in the pathogenesis of hepatic encephalopathy. Brain accumulation of aromatic amino acids may induce a profound change in neurotransmitters' synthesis leading to hepatic encephalopathy. The administration of branched chain amino acids may improve hepatic encephalopathy either by reducing aromatic amino acid outflow from muscle proteins or by inhibiting their brain uptake through direct competition for a common carrier.

In chronic liver failure the severe catabolic state and the consequent degradation of body protein are the major determinants of the characteristic amino acid imbalance with increased aromatic amino acid, phenylalanine, tyrosine, tryptophan, and decreased branched chain amino acid, valine, leucine, isoleucine values (Fig. 1).¹

As aromatic amino acid and branched chain amino acid are transported into the brain through a common carrier system in the blood brain barrier,² brain uptake of aromatic amino acid may be favoured by the reduction in plasma branched chain

amino acid values. According to the hypothesis advanced by Fischer and Baldessarini in 1971,³ brain accumulation of aromatic amino acid may lead to a change in the synthesis of neurotransmitters, resulting in a depletion of putative neurotransmitters such as norepinephrine and dopamine, and an increased synthesis of false or weak neurotransmitters such as octopamine and phenylethanolamine and the inhibi-

Fig. 1 Plasma amino acid pattern in chronic liver failure.

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tory neurotransmitter serotonin. Such a disturbance in neurotransmitter synthesis is thought to be responsible for the neurological disorders and coma seen in patients with chronic liver failure.

The part played by aromatic amino acid in the pathogenesis of hepatic encephalopathy has recently been confirmed by the finding that in normal dogs brain perfusion through the carotid arteries with a solution containing phenylalanine and tryptophan was followed within six hours by a reversible, hepatic like coma,⁴ accompanied by a clinically important rise in cerebrospinal fluid concentrations of phenylalanine, tryptophan, tyrosine, octopamine and phenylethanolamine (Fig. 2). In a later series of

Fig. 2 Clinical, electroencephalographic, and cerebrospinal fluid biochemical modifications during intracarotid infusion of phenylalanine and tyrosine in normal dogs.

experiments, using the same experimental model, it was shown that hepatic like coma induced by phenylalanine and tryptophan could be totally prevented by simultaneous infusion of the three branched chain amino acids.⁴ As a possible consequence of their characteristic regulatory influence on muscular protein turnover,⁵⁻⁷ branched chain amino acids have been shown to be particularly effective in reducing plasma concentrations of aromatic amino acid in chronic liver failure⁸ (Table 1). Branched chain amino acids should therefore be effective in the treatment of hepatic encephalopathy. They are thought to be able to interrupt the chain of events linking the hypercatabolic state to hepatic encephalopathy in at least three possible ways (Fig. 3): (i) They reduce protein breakdown and stimulate protein synthesis, (ii) they normalise the plasma amino acid pattern either by decreasing proteolysis or by increasing the use of aromatic amino acid for protein synthesis, (iii) they provide the bulk of competition across the blood brain barrier, thus preventing aromatic amino acid from accumulating in the brain.

Clinical studies

To test the clinical efficacy of branched chain amino acid in the treatment of hepatic encephalopathy two consecutive studies were carried out in patients with cirrhosis and severe encephalopathy (grade 3-4).⁹⁻¹⁰ In the preliminary uncontrolled study⁹ 19 patients with grade 3-4 hepatic encephalopathy received an intravenous solution containing branched chain amino acid alone (leucine 11 g/l, isoleucine 9 g/l, valine 8.4 g/l) in 20% dextrose. The solution was delivered at a constant rate of 60 ml/hour for 24 hours, thereafter at 80 ml/hour by means of a peristaltic pump. Precipitating events received appropriate treatment, but no specific treatment for

Table 1 Variations (mean(SE)) of plasma amino acid concentrations during glucose (solution A) or glucose + branched chain amino acid (solution B) infusion.

	Preinfusion	One hour	Three hours	Six hours	12 hours	24 hours	Postinfusion
Phenylalanine							
Solution A	1.26 (0.16)	1.01 (0.16)	1.01 (0.13)	0.95 (0.11)	1.01 (0.13)	0.91 (0.08)	1.28 (0.15)
Solution B	1.54 (0.32)	1.13 (0.25)	0.51 (0.15)	0.58 (0.10)	0.45 (0.07)	0.65 (0.05)	1.45 (0.20)
Total tryptophan							
Solution A	0.90 (0.20)	0.77 (0.12)	0.92 (0.16)	0.73 (0.07)	0.82 (0.17)	0.71 (0.11)	0.87 (0.08)
Solution B	1.01 (0.21)	0.82 (0.13)	0.73 (0.13)	0.50 (0.13)	0.52 (0.09)	0.46 (0.10)	0.81 (0.23)
Free tryptophan							
Solution A	0.14 (0.01)	0.12 (0.02)	0.08 (0.01)	0.09 (0.02)	0.09 (0.01)	0.09 (0.01)	0.09 (0.02)
Solution B	0.14 (0.01)	0.11 (0.01)	0.08 (0.01)	0.05 (0.01)	0.04 (0.01)	0.04 (0.01)	0.15 (0.01)
Tyrosine							
Solution A	2.34 (0.24)	1.87 (0.17)	1.79 (0.16)	1.68 (0.16)	1.78 (0.20)	1.65 (0.23)	2.07 (0.17)
Solution B	2.37 (0.15)	2.07 (0.19)	1.47 (0.24)	1.20 (0.21)	1.00 (0.14)	0.80 (0.06)	2.11 (0.17)

Fig. 3 Possible interference of branched chain amino acid on chain of events leading to hepatic encephalopathy.

hepatic encephalopathy was given. Complete recovery of the mental state – that is, grade 0 hepatic encephalopathy – was obtained in all patients two and a half to 48 hours (mean 20.5 (SE) 3.75). The time of arousal was closely related to the severity of the events that had precipitated encephalopathy (Fig. 4).

Encouraged by the favourable results of this preliminary study, a prospective controlled study was undertaken, in which the efficacy of the branched chain amino acid in 20% dextrose was compared with that of lactulose.¹⁰ Early criteria included the presence of liver cirrhosis, grade 3–4 hepatic encephalopathy, and the absence of hepatorenal syndrome.

Forty patients were randomly allocated to receive either branched chain amino acid or lactulose. Both groups were given intravenous glucose in isocaloric amounts. Precipitating events received appropriate treatment. Based on the results of the previous study,⁹ a time limit of 48 hours was fixed to assess

the efficacy of the treatment. If mental recovery occurred within 48 hours treatment was continued for a further 48 hours and then discontinued. Thereafter, patients in both groups received a protein restricted diet plus lactulose in sufficient amounts to ensure a cathartic effect. If mental recovery did not occur within 48 hours the two treatments were combined. Mental recovery was considered to have occurred when the patients regained consciousness – that is, grade 0 hepatic encephalopathy, according to the classification of Adams and Foley.¹¹

Three patients in each group were lost from the study, the data therefore refer to 34 patients. The two groups were comparable as far as sex, type of cirrhosis, precipitating events and liver function tests were concerned.

Table 2 shows the clinical results. Twelve of the 17 patients (70.6%) receiving branched chain amino acid regained consciousness in a mean time of 27.6 (6–48) hours. In the group receiving lactulose eight of the seventeen patients (47%) were fully alert in a mean time of 31.5 (4–4) hours.

Using the χ^2 test, the difference in the recovery rate between the two groups was not significant. This notwithstanding, the clinical results of this study clearly indicate that intravenous branched chain amino acids are at least as effective as lactulose in reversing hepatic coma.

Fig. 4 Time of arousal related to precipitating factors observed in 19 patients with grade 3–4 hepatic encephalopathy receiving intravenous branched chain amino acids.

Table 2 Clinical results in 34 patients included in study

	Treatment A (Branched chain amino acid + glucose)	Treatment B (Lactulose + glucose)
No of patients	17	17
Responsive	12 (70.6%)	8 (47.1%)
Unresponsive	5 (29.5%)*	9 (52.9%)†

* Three patients died from bleeding; two patients received the combined treatment.

† Two patients died from bleeding; one from hepatorenal syndrome; one from acute liver necrosis; five patients received the combined treatment.

Fig. 5 Plasma aromatic amino acid and branched chain amino acid behaviour in patients with hepatic encephalopathy receiving intravenous branched chain amino acid.

In this study blood samples for determining amino acid were drawn before starting treatment, on mental recovery, six hours after the treatment was discontinued, and at the end of the study. Fig. 5 shows the behaviour of plasma aromatic amino acid and branched chain amino acid in the patients treated with branched chain amino acid. Phenylalanine, tyrosine, and tryptophan, which were high when patients were in coma, fell to normal limits on mental recovery. It was surprising and also puzzling to observe that, with the exception of free tryptophan, aromatic amino acid and branched chain amino acid had returned to pretreatment values at the tenth day, when patients had no evidence of encephalopathy.

The significant correlation between plasma free tryptophan concentrations and the mental state provides corroborative evidence for the role of raised tryptophan concentration in the pathogenesis of hepatic encephalopathy. It must also be appreciated, however, that changes in plasma concentrations do not necessarily reflect changes in brain concentrations. To investigate the false neuro-

Fig. 6 Plasma and cerebrospinal fluid amino acid pattern in patients with hepatic encephalopathy receiving intravenous branched chain amino acid.

transmitter hypothesis further it was decided to monitor simultaneously amino acid and biogenic amine concentrations both in plasma and cerebrospinal fluid. Fourteen patients with grade 3–4 hepatic encephalopathy received branched chain amino acid, using the same modalities as those in the previous study. Plasma and cerebrospinal fluid amino acid and amine concentrations were determined only in the 10 patients who regained consciousness.¹² The amino acid pattern was found to be quite different in cerebrospinal fluid and plasma (Fig. 6). Cerebrospinal fluid concentrations of tyrosine and tryptophan had decreased considerably by the time the patients regained consciousness and remained within the normal range by the tenth day. By contrast, although plasma concentrations of tyrosine and tryptophan fell when consciousness was regained, 10 days later they had increased again (Fig. 6). These findings are mirrored by the finding that the concentrations of octopamine and phenylethanolamine in cerebrospinal fluid had also fallen on regaining of consciousness (Fig. 7).¹³

The data presented argue strongly in favour of a therapeutic effect of branched chain amino acid in the treatment of hepatic coma in patients with

chronic liver disease. Branched chain amino acids are likely to act via two distinct mechanisms; firstly, by inhibiting transport of aromatic amino acid across the blood brain barrier; and secondly, by reducing aromatic amino acid and ammonia outflow from muscles as a consequence of their regulatory effects on muscular protein turnover.

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Fig. 7 Cerebrospinal fluid, octopamine, and phenylethanolamine concentrations in patients with hepatic encephalopathy receiving intravenous branched chain amino acid.