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Branched chain amino acids in liver disease: fact or fantasy?

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It has been recognised for many years that patients with chronic parenchymal liver disease are malnourished. In a recent report O'Keefe *et al* found that on formal testing a considerable number of their patients had clinical, biochemical, haematological and immunological variables thought to be indicative of protein calorie malnutrition,[1] and furthermore, their data suggested a link between malnutrition, energy, sepsis and mortality in their patients.[1]

Poor dietary intake is almost certainly one of the principal causes of nutritional deficiencies in chronic liver disease. This may arise on account of associated anorexia and nausea and also because dietary protein intake is often restricted for therapeutic reasons as part of the management of hepatic encephalopathy.

Evidence is accumulating, which suggests that nutritional deficiencies also arise on account of impaired digestion and absorption of nutrients. To date, pancreatic exocrine insufficiency has been shown in patients with cirrhosis,[2] as well as malabsorption of D-xylose, thiamine, folic acid and fat.[3]

Specific changes in whole body protein turnover rates may also contribute to the impaired nutritional state seen in patients without cirrhosis. Thus although whole body protein synthesis rates in cirrhosis seem to be normal, rates of breakdown are increased in patients with and without encephalopathy.[4]

Hepatic encephalopathy: the dilemma

It is a feature of the natural history of the disease that most patients with hepatic cirrhosis will develop hepatic encephalopathy and coma at some stage during the course of their illness. The commonest precipitating causes are infection, electrolyte abnormalities (often caused by diuretic abuse), variceal haemorrhage, sedative abuse and constipation.

One of the greatest dilemmas in clinical hepatology is that of often being forced to restrict protein intake in an already malnourished patient with cirrhosis in an attempt to improve or prevent the onset of hepatic encephalopathy. While the mental state of these patients may improve by dietary protein restriction, their nutritional state may deteriorate. Periodically malnutrition may be one of the reasons why these patients are unduly susceptible to developing infection and, as is widely known, infection is one of the most common precipitating causes of hepatic encephalopathy.[6]

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NUTRITIONAL SUPPORT IN THE ABSENCE OF HEPATIC ENCEPHALOPATHY

When there is no impairment of mental function the nutritional state of malnourished patients with parenchymal liver disease can be improved by standard means. Whenever possible, this should be done by increasing normal dietary intake with appropriate supplementation with electrolytes, vitamins, and haematinics. If for any reason nutrients cannot be given in the form of a normal diet then these patients should receive nutritional support via the enteral or parenteral route. The normal principles for determining whether nutritional support should be provided by the enteral or parenteral route should be adhered to and, in general, as long as gastrointestinal function is normal or near normal, attempts should be made to provide nutritional support via the enteral route, and the use of parenteral nutrition should be restricted to those patients whose gastrointestinal function is severely impaired.

NUTRITIONAL SUPPORT IN THE PRESENCE OF HEPATIC ENCEPHALOPATHY

Although the pathogenesis of hepatic encephalopathy has not been fully elucidated, for many years high serum concentrations of ammonia have been thought to play a major part and accordingly the rationale of standard "anti-coma" treatment has been to lower serum ammonia concentrations. A major source of ammonia formation is colonic bacterial ureolysis, and the cornerstone of treatment –

namely, protein restriction – has been aimed at reducing the rate of urea synthesis, treatment with neomycin, lactulose, or lactitol[6 7] being aimed at further reducing the colonic production and absorption of ammonia.

In practice, therefore, many comatosed patients receive peripheral infusion of 10% dextrose as their sole source of energy and a maximum of 20 g protein via a nasogastric tube as their sole source of nitrogen, vitamin supplementations usually being given in the form of daily Parentrovite injections. If the patient has ascites volume intake may be restricted to 1·0–1·5 l/day, so that total energy intake may be as low as 400 kcal/day. The net result of this standard approach is that it has not only been impossible to improve the nutritional state of the malnourished and encephalopathic patients with cirrhosis, but as implied above, the nutritional state of these patients actually deteriorates during treatment.

During the past decade much research has been directed towards examining the role of altered amino acid metabolism in the pathogenesis of hepatic encephalopathy, in particular, the relation between imbalances of plasma amino acid profiles and brain false neurotransmitter synthesis. New approaches to the management of malnutrition and treatment of the encephalopathy in patients with cirrhosis have emerged, based on the use of branched chain enriched amino acid formulations. The aim of this paper is to discuss some of the basic research that has promoted the new approaches to treatment and to review results of trials that report clinical experiences.

The role of circulating amino acid balances in the pathogenesis of hepatic encephalopathy

A complete review of the biochemical mechanisms thought to have a role in the pathogenesis of hepatic encephalopathy is not relevant to the ensuing discussion, and the reader is referred elsewhere for this.[8]

Hepatic failure is associated with a considerable increase in plasma concentrations of aspartate, glutamate, phenylalanine, tyrosine, methionine and free tryptophan.[8] Most attention has been focused on phenylalanine and tyrosine because of the precursor association with brain catecholamines, and on tryptophan, which is converted into the inhibitory neurotransmitter serotonin.

In chronic encephalopathy there is a two to four-fold rise in the plasma concentrations of the aromatic amino acids, together with a decrease in the plasma concentrations of the branched chain amino acids valine, leucine, and isoleucine.[9] A combination of catabolism and impaired hepatocellular function is probably responsible. Raised plasma concentrations of glucagon stimulate muscle catabolism with release of amino acids for gluconeogenesis.[10] When hepatic function is poor, however, the uptake and metabolism of plasma aromatic amino acids is impaired. In contrast, branched chain amino acids are preferentially metabolised in muscle and fat, and their low values can be explained by their enhanced uptake as a result of the hyperinsulinaemia.[11] Concentrations of the aromatic amino acids are considerably raised in fulminant hepatic failure, but concentrations of branched chain amino acids are normal.[12] This pattern is thought to arise largely from massive necrosis of liver cells with release of amino acids into the circulation; catabolism probably has a less important role.

RELATION TO FALSE NEUROTRANSMITTER HYPOTHESIS

Increased intracerebral concentrations of phenylalanine and tyrosine may result in the formation of "false neurotransmitter" amines, which are thought to displace the putative neurotransmitters from synaptosomes. Excess tyrosine is decarboxylated to tyramine, which is then converted by dopamine-B-oxidase into octopamine, and phenylalanine is converted into phenylethylamine and thence into phenyethanolamine. Concentrations of octopamine and phenylethanolamine were found to be raised in the brains of animals in acute hepatic coma.[13] Phenylalanine also competes with tyrosine for the enzyme tyrosine hydroxylase, and tyramine competes with dopamine for dopamine-B-oxidase, with the result that intracerebral formation of the normal stimulatory transmitters (dopamine and noradrenaline) may be reduced.[14]

Concentrations of amino acids in the brain depend on the integrity of the blood brain barrier and the activity of the carrier systems of amino acids, as well as on the plasma concentrations. The neutral amino acids are transported across the blood brain barrier by a common carrier,[15] and there is usually competition between the aromatic and branched chain amino acids.[16] Thus low circulating concentrations of branched chain amino acids, together with their lower affinity constants for the carrier, might be expected to favour transport into the brain of the aromatic amino acids. Concentrations of branched chain amino acids in the cerebrospinal fluid have been observed to be normal in animals during hepatic coma, despite low plasma concentrations,[17] possibly as a result of increased activity of the carrier system.[18]

In acute liver failure the blood brain barrier is

commonly disrupted and may enhance the cerebral effect of plasma amino acid imbalance. Zaki *et al*,[19] by means of the Oldendorf technique, showed that the blood brain barrier is also disrupted in rats six weeks after a portacaval anastomosis. Brain uptake of L-(^{14}C) glucose, D-(^{14}C) sucrose, and (^{14}C) insulin, substances which do not normally cross the blood brain barrier were all increased, in addition to a selective increase in the uptake of neutral amino acids.

Further supportive evidence for a role of the aromatic amino acids in the pathogenesis of hepatic encephalopathy has arisen from a potentially important study in normal dogs.[20] Intracarotid infusion of 1% tryptophan and 1% or 1·5% phenylalanine resulted in a neurological deterioration clinically, which resembled hepatic encephalopathy, culminating in coma. When a branched chain amino acid mixture (0·63% leucine+0·4% isoleucine+0·46% valine) was added to the infusate, coma did not occur. The data were interpreted on the basis that the addition of branched chain amino acids may have prevented coma by competing with the aromatic acids for transport across the blood brain barrier.[20]

It seems increasingly clear that a unified hypothesis to explain the pathogenesis of hepatic encephalopathy in cirrhosis is untenable. In their more recent hypothesis Fischer *et al*[21] proposed that hyperammonaemia increases the influx of ammonia into the brain where it reacts with glutamic acid to form glutamine, which then effluxes from the brain using the same carrier system that mediates the influx into the brain of the other neutral amino acids that are the precursors for synthesis of the false neurotransmitters. Thus there may be a link between the ammonia toxicity and the false neurotransmitter hypothesis.[21]

Against the theory of the false neurotransmitter is that octopamine instilled into the ventricles of rats produced a striking increase in its concentration in the brain and a fall in whole brain dopamine and noradrenaline to one tenth of normal values, without any disturbance in consciousness.[22] In a study in which brain catecholamines were measured after death in patients with cirrhosis and encephalopathy no reduction in dopamine or noradrenaline concentrations was found, and octopamine concentrations were decreased compared with those of patients with cirrhosis who were not encephalopathic at the time of death.[23]

Branched chain amino acid treatment of hepatic encephalopathy

Fischer *et al* were the first to propose that the primary treatment of hepatic encephalopathy in cirrhosis might be enhanced by normalising circulating amino acid profiles in their patients.[24] Subsequently, some would argue that the emphasis of this approach has shifted from primary treatment of the encephalopathy to the safe provision of nutritional support, which at the same time does not have the expected deleterious effect on the neuropsychiatric state of these patients. Fischer's group devised a specially formulated amino acid solution for intravenous use that contained considerably decreased amounts of phenylalanine, tyrosine, tryptophan, methionine and glycine and increased amounts of the branched chain amino acids leucine, isoleucine, and valine, as well as arginine. After showing that survival in encephalopathic dogs receiving this formulation was appreciably increased compared with dogs receiving a standard intravenous formulation of amino acids,[25] clinical studies were started.

Results were encouraging, for not only did infusion of the amino acid mixture correct plasma amino acid profiles of patients, but neuropsychiatric state seemed to improve during treatment.[26] In passing, they found that positive nitrogen balance was achieved.[26]

The studies conducted by Fischer[26] have been criticised because they were not controlled. The composition of amino acid solution devised by Fischer *et al* (FO80) was based purely on extrapolations made from experimental data derived from their animal and clinical studies. In retrospect, certain aspects of the formulation are open to criticism. With the aim of normalising the plasma amino acid profile of the patients with hepatic encephalopathy, 34·6% of the amino acid content of FO80 was constituted with branched chain amino acids (leucine 13·4%, valine 10·2%, isoleucine 11·0%). Later studies have shown that it is the intravenous infusion of leucine, rather than valine, or isoleucine that lowers the concentrations of the aromatic amino acids and methionine.[27] It can be argued, therefore, that the proportions of the individual branched chain amino acids are not necessarily ideal in the formulation. FO80 contains no tyrosine or cysteine, and in some patients with cirrhosis this has been shown to prevent achievement of positive nitrogen balance despite provision of adequate essential amino acid precursors.[28] Finally, the rationale for infusing tryptophan, phenylalanine, and methionine in patients with hepatic encephalopathy, even in small amounts, is questionable.[29]

Interpretation of the results of the clinical studies[29] is also confused because FO80 contains relatively high proportions of arginine (7·5%). There is evidence to suggest that arginine (or

ornithine, the precursor as well as the metabolic product of arginine), may counteract hyperammonaemia by stimulating ureagenesis.[30] It cannot be concluded with certainty, therefore, that the beneficial clinical responses attributed to FO80 are not due to the increases in arginine content.

As mentioned above, the studies by Fischer have stimulated much further clinical research into mixtures of amino acids rich in branched chain amino acids and deficient in aromatic amino acids. Conn[31] pointed out how difficult it is to draw conclusions from the data, particularly those derived from uncontrolled trials. The controlled trials that have been performed have, moreover, evaluated different amino acid mixtures administered in different ways, using different end products, to patients with different types and degrees of encephalopathy. Not surprisingly, different results were obtained. Can any conclusions be drawn about the therapeutic efficacy of branched chain amino acids in portal systemic encephalopathy? In my opinion the answer to this is a qualified "yes," but only if certain ground rules are accepted. Firstly, only controlled trials must be considered, and secondly, it is inappropriate to compare directly results of studies carried out in patients with cirrhosis who present with clearly different clinical types of encephalopathy – that is, latent, chronic, and acute forms.

The ensuing analysis has been restricted to seven controlled trials that have been reported fully in English or American scientific journals.[31–37] One of these studies was restricted purely to patients with latent (subclinical) portal systemic encephalopathy,[36] three to patients with chronic portal systemic encephalopathy,[31–33] and three patients with acute portal systemic encephalopathy.[34 35 37]

1 LATENT (SUBCLINICAL) PORTAL SYSTEMIC ENCEPHALOPATHY (Table 1)

Egberts *et al* are the only group to have restricted their studies to patients with cirrhosis who have never been clinically encephalopathic (all grade 0) and who have never received dietary restriction as part of clinical management.[36] Latent (subclinical) portal systemic encephalopathy was diagnosed using an extensive psychometric test programme.

Patients received a defined diet of 35 cal/kg a day containing 1 g of protein/kg/day. Branched chain amino acids or casein in a dose of 0·25 g/kg a day was also given in a cross over fashion for one week. Semiquantitative nitrogen balance increased during both treatments, with a tendency of a larger increase during branched chain amino acid treatment. At the same time ammonia concentration tended to decrease during branched chain amino acid treatment. Taking into account the crossover design, appreciable improvements attributable to branched chain amino acid treatment could be shown in psychomotor functions (line tracing, tapping, steadiness, auditory reaction time), attention (digit table), and practical intelligence (digit symbol, number connection test).

It must be appreciated that the study only lasted one week so that the benefits shown must be considered at best to be very short term.

Table 1 *Controlled trial of branched chain amino acids in latent (subclinical) portal systemic encephalopathy*†

From Egberts *et al*[36]	
Trial design	Double blind cross over (n=22)*
Method of administration	Oral
Duration of treatment	7 days
Test	Dietary protein 1g/kg^{-1}/day^{-1} + BCAA 0·25 g kg^{-1}/day^{-1} (Leucine 43% valine 28·5% isoleucine 28·5%)
Control	Dietary protein 1 g/kg^{-1}/day^{-1} + Casein 0·25 g/kg^{-1}/day^{-1}
Nitrogen balance	Positive both groups
Encephalopathy	Improvement Test *v* control

†Analysis restricted to studies published in full in English language scientific journals.
*14/22 patients received lactulose throughout both study periods.

2 CHRONIC PORTAL SYSTEMIC ENCEPHALOPATHY (Table 2)

Three groups have addressed the question of whether branched chain amino acid supplementation has a beneficial effect on the mental state of patients with cirrhosis and chronic portal systemic encephalopathy.[31–33] Two trials, each with a small number of patients, were cross over in design[32 33] and the third was a larger double blind randomised trial.[31] Entry criteria differed in that in the cross over trial of Eriksson *et al*[32] all patients had clinical encephalopathy (grade I–II) on entry, although only four of seven were receiving a 40 g protein restricted diet. All patients in the two other trials[31 33] were on a 40 g protein restricted diet on account of chronic portal systemic encephalopathy and were either in grade 0 or stable grade I encephalopathy on entry.

These important differences in trial design and entry criteria make it impossible directly to compare results. Furthermore, as Table 2 shows, branched chain amino acid supplements were administered in the pure form in one trial[32] and as the amino acid diet Hepaticaid in the two others.[31 33]

In neither of the two small and short term cross over trials[32 33] was there a suggestion that branched chain amino acid supplements had any appreciably

Table 2 *Controlled trials of branched chain amino acids in chronic portal systemic encephalopathy**

Reference	Eriksson *et al*[32]	McGhee *et al*[33]	Horst *et al*[31]
Trial design	Double blind randomised crossover (n=7)	Randomised cross over (n=4)	Double blind randomised (n=17 for test) (n=20 for controls)
Coma grade on entry	I–II	0†	0–1†
Method of administration	Oral	Oral	Oral
Duration of treatment	14 days‡	11 days‡	4 weeks
Treatment			
Test	Dietary protein (40–100 g/day^{-1})+ BCAA (leucine 2 g, valine 6 g, isoleucine 3 g)	20 g casein diet + 30 g BCAA enriched amino acid diet (Hepaticaid; leucine 4·0 g, valine 3·1 g, isoleucine 3·3 g)	Week 1 20 g dietary protein Week 2 20 g dietary protein + 20 g BCAA enriched amino acid diet (Hepaticaid, leucine 13·4%, valine 10·2%, isoleucine 11·0%) Week 3 20 g dietary protein + 40 g hepaticaid Week 4 20 g dietary protein + 60 g hepaticaid
Control	Dietary protein (40–100 g/day^{-1}) + placebo (four patients on 40 g protein restriction also maintained on lactulose throughout both study periods)	Casein diet (50 g)	Week 1 20 g dietary protein Week 2 40 g dietary protein Week 3 60 g dietary protein Week 4 80 g dietary protein
Results			
Nitrogen balance		Positive	Positive both groups weeks 3 and 4
Encephalopathy	NS	NS	Frequency of encephalopathy greater in test *v* control patients

†All had had chronic recurrent portal systemic encephalopathy and had required restriction of protein to 40 g/day^{-1} or less.
*Analysis restricted to studies published in full in English language scientific journals.
‡Duration of treatment for each study period.

beneficial effect on the mental state of the patients studied.

In the longer term and larger trial of Horst *et al*[31] there seemed to be a distinct advantage of the branched chain amino acid supplemented diet, Hepaticaid. Thus although Hepaticaid was equally effective at inducing positive nitrogen balance as an equivalent amount of whole protein, encephalopathy was induced far less often during the four weeks of the trial.[31] If these observations are confirmed (and they were not made in the cross over study of McGhee *et al*[33]) then the potential role of branched chain amino acids in chronic portal systemic encephalopathy will have shifted from that of a primary therapeutic agent for the encephalopathy to a means of more safely improving the nutritional state of these patients: a clear change of emphasis compared with the original claims.

3 ACUTE PORTAL SYSTEMIC ENCEPHALOPATHY (Table 3)

In three simple randomised controlled trials[34 35 37] branched chain amino acids were administered parenterally. It is difficult to compare the results of all three directly, because in the two earlier trials[34 35] branched chain amino acids represented the sole source of nitrogen, whereas in the third[37] the branched chain amino acids enriched amino acid solution FO80 was given. The three trials examined two end points – namely, the effect on encephalopathy and effect on mortality.

In the trials conducted by Rossi-Fanelli and Wahren[34 35] no significant benefit of branched chain amino acids was seen either in respect of encephalopathy or mortality. The trials were very similar in design except that Rossi-Fanelli *et al*[34] entered their encephalopathic patients into the trial immediately, whereas patients in the Wahren trial were treated by standard means for 24 hours before randomisation.[35] (Table 3) Control patients in the Rossi-Fanelli trial[34] received lactulose whereas those in the other trial[35] did not. It should be emphasised that in both trials considerable quantities of glucose were given to both the test and control patients (less in the

Table 3 *Controlled trials of branched chain amino acids in patients with cirrhosis and acute portal systemic encephalopathy†*

Reference	Rossi-Fanelli *et al*[34]	Wahren *et al*[35]	Cerra *et al*[37]
Trial design	Open randomised	Double blind randomised	Double blind randomised
Test patients	(n=17)	(n=25)	(n=40)
Control patients	(n=17)	(n=25)	(n=35)
Coma grade on entry	3–4	2–4	2–4
Duration of previous medical treatment	None	23·5 (SE 35) hours (test patients) 25·5 (SE 30) hours (control patients)	48 hours
Method of administration	Parenteral	Parenteral	Parenteral
Duration of treatment	2–4 days	One day after grade 0–1 or maximum 5 days	Four to 14 days
Treatment			
Test	1600 kcal/day^{-1} (glucose) + BCAA 56·8 g Leucine 22·0 g Valine 16·8 g Isoleucine 18·0 g	30 kcal/kg^{-1}/day^{-1}* (glucose 50% fat emulsion 50%) + BCAA 40 g Leucine 28·0 g Valine 8·0 g Isoleucine 4·6 g + Glucose 400 kcal/day^{-1}	25 kcal kg^{-1}/day^{-1} (glucose) + FO80 BCAA 22–30 g Leucine 8·5–11·6 g Valine 6·5–8·9 g Isoleucine 7·0–9·5 g
Control	1600 kcal/day^{-1} (glucose) + Lactulose	30 kcal/kg^{-1}/day^{-1}* (glucose 50% fat emulsion 50%)	27 kcal/kg^{-1}/day^{-1} (glucose) + Neomycin
Encephalopathy end point	Grade 0	Grade 0–2	Rate of diminution of encephalopathy grade
Results			
Nitrogen balance	Not measured	Not measured	Significant test *v* control patients
Encephalopathy	NS	NS	Significant test *v* control patients days 1–2 only
Mortality (days after entry)	10	5 25	21 Discharge
Test	29%	40% 70%	35% 42·5%
Control	53%	20% 70%	63% 65·0%
	NS	NS NS	p<0·01 p<0·01
Exclusion criteria	Renal failure	Renal failure Respiratory failure Septic shock	Renal failure Severe fluid restriction Significant gastrointestinal bleeding

†Analysis restricted to studies published in full in English language scientific journals.
*Eight patients (five test, three control) received lactolose or neomycin, or both.

Wahren trial.[35]) On a theoretical basis glucose infusion would be expected to raise circulating insulin concentrations, which in turn would be expected to promote uptake of branched chain amino acids into muscle, thereby lowering even further circulating branched chain amino acid concentrations.

According to the hypothesis under investigation this might be expected to worsen the encephalopathy, thereby biasing the results toward the test group. As there were no apparent benefits of parenterally administered branched chain amino acids (40–56·8 g d^{-1}) in either or both test groups there would seem to be no justification for recommending the use of pure branched chain amino acid supplements in combination with glucose[34] or glucose plus lipid[35] in patients with cirrhosis who develop episodes of acute encephalopathy, either on a scientific or cost effective[38] basis.

At first sight the results of the Cerra trial[37] are promising: a significantly beneficial effect of a parenterally administered branched chain amino acid enriched (22–30 g d^{-1}) amino acid mixture (FO80) on encephalopathy and mortality was claimed. With respect to encephalopathy, the differences were only significant between days 1 and 2, and, if Cerra *et al*[37] had taken the same encephalopathy end point as Rossi-Fanelli *et al*[34] and Wahren *et al*,[35] their difference would probably have not been significant. On balance, therefore, it seems premature to conclude that FO80 has a clinically important effect on acute episodes of encephalopathy in patients with cirrhosis. It is difficult, however, to get away from the fact that the

mortality was lower in the group of patients receiving FO80 than in control patients.

Unlike the studies of Rossi-Fanelli *et al*,[34] and Wahren *et al*,[35] Cerra *et al* excluded patients whose encephalopathy was precipitated by significant gastrointestinal haemorrhage.[37] Whether this influenced the results is difficult to say. Bleeding from oesophageal varices carries a high mortality[39,40] and it is possible that if, as in the two other trials, such patients had been included, different results may have been obtained. Cerra *et al* did treat their control patients with neomycin[37] so it can be concluded, albeit on the basis of a single trial, that intravenous infusion of FO80 in encephalopathic cirrhotic patients, whose coma had not been precipitated by significant gastrointestinal haemorrhage, confers a clinically significant benefit in respect of mortality. Whether the observed improvement in mortality was related merely to the provision of nutritional support or to the effect of branched chain amino acids per se cannot be determined, and further controlled trials with FO80 or related amino acid mixture are clearly required.

Conclusion

Further long term studies are required before any firm conclusions can be drawn about the clinical benefits of branched chain amino acid supplementation in patients with subclinical or latent encephalopathy. In patients with established chronic portal systemic encephalopathy branched chain amino acid supplemented amino acid mixtures seem to induce positive nitrogen balance to about the same degree as an equivalent amount of dietary protein, without inducing encephalopathy as often. Infusions of branched chain amino acids alone in patients with cirrhosis and acute encephalopathy do not seem to confer any advantage either in terms of encephalopathy or survival. In contrast, there is a suggestion that survival in the patients can be improved by administering a branched chain amino acid enriched amino acid mixture (FO80), at least if the encephalopathy is not precipitated by significant gastrointestinal haemorrhage.

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