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ORIGINAL PAPER

The treatment of hepatic encephalopathy

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Abstract Current recommendations for the treatment of hepatic encephalopathy are based, to a large extent, on open or uncontrolled trials, undertaken in very small numbers of patients. In consequence, there is ongoing discussion as to whether the classical approach to the treatment of this condition, which aims at reducing ammonia production and absorption using either non-absorbable disaccharides and/or antibiotics, should be revisited, modified or even abandoned. Pros and cons of present therapeutic strategies and possible future developments were discussed at the

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fourth International Hannover Conference on Hepatic Encephalopathy held in Dresden in June 2006. The content of this discussion is summarized.

Keywords Branched-chain amino acids · Bromocriptine · Hepatic cirrhosis · Hepatic encephalopathy · Non-absorbable antibiotics · Non-absorbable disaccharides · Ornithine aspartate · Sodium benzoate · Treatment · Zinc

Introduction

Hepatic encephalopathy is a complex neuropsychiatric syndrome, which, in patients with cirrhosis, manifests as a spectrum of change, that may or may not be clinically apparent. It has been shown convincingly that the presence of hepatic encephalopathy, (1) has a detrimental effect on the overall quality of life; (2) most probably impairs the execution of complex tasks such as driving; (3) has a significant negative effect on survival; and (4) when clinically overt, is an indication for liver transplantation.

The pathogenesis of hepatic encephalopathy is unknown, but there is general agreement that, in the majority of instances, it reflects a metabolic, rather than a structural disorder of the brain. It is unlikely than any one abnormality is responsible for the genesis of this syndrome, although gut-derived nitrogenous compounds, specifically ammonia, are thought to play a major role by inducing alterations in cerebral neurotransmitter balance, especially at the astrocyte–neurone interface.

Treatment of hepatic encephalopathy has, in consequence, been directed primarily at reducing the production and absorption of gut-derived neurotoxins, particularly ammonia, primarily through use of non-absorbable disaccharides and non-absorbable antibiotics. However, this rather empirical approach to treatment has recently come under scrutiny for a number of reasons: (1) a systematic Cochrane review questioned the efficacy of these agents, pointing out that there is insufficient high-quality evidence to support their use; (2) interest in the inter-organ trafficking of ammonia has highlighted other potential targets for reducing circulating ammonia concentrations (Fig. 1); and (3) other pathophysiological mechanisms have been identified, for example, systemic inflammation, which may provide additional potential targets for treatment.

This review is based, in large part, on opinions expressed at a symposium on ‘The Treatment of Hepatic Encephalopathy’ held during the fourth International Hannover Conference on Hepatic Encephalopathy in Dresden in June 2006.

Non-absorbable disaccharides

The non-absorbable disaccharide lactulose was first introduced in 1966 (Bircher *et al.* 1966) and is probably the most widely used agent for the treatment of hepatic encephalopathy. Lactitol was introduced into clinical practice in the mid-1980s.

Non-absorbable disaccharides are not absorbed in the small intestine but pass unchanged into the large intestine where they are extensively metabolised by colonic bacteria, first to their constituent monosaccharides and then to volatile fatty acids and hydrogen. Their beneficial effects reflect their ability to reduce the intestinal production/absorption of ammonia, which is achieved in three major ways (Conn

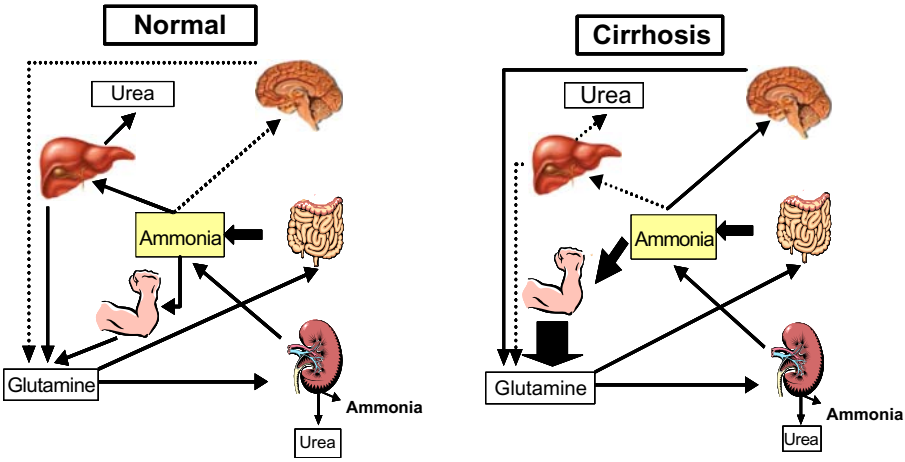

Fig. 1 Inter-organ trafficking of ammonia in healthy individuals and in patients with in cirrhosis. Under normal circumstances ammonia is detoxified in the liver. In patients with cirrhosis, the metabolic capacity of the liver is exceeded resulting in an increase in circulating ammonia. Under these circumstances the surplus ammonia is detoxified in muscle with the production of glutamine; this is in turn broken down to ammonia by glutaminase in enterocytes or else excreted by the kidney as ammonia (modified from Shawcross and Jalan 2005)

and Lieberthal 1979). (1) A laxative effect: the colonic metabolism of these sugars results in an increase in intraluminal gas formation, an increase in intraluminal osmolality, a reduction in intraluminal pH, and an overall increase in transit time which reduces the period available for ammonia absorption; (2) uptake of ammonia by bacteria: the intraluminal changes in pH result in a leaching of ammonia from the circulation into the colon; the colonic bacteria use the released volatile fatty acids as substrate and, in consequence, proliferate incorporating, as they do, the trapped colonic ammonia as a nitrogen source for protein synthesis; the increase in bacterial numbers additionally 'bulks' the stool and contributes to the cathartic effect; (3) reduction of ammonia production by the small intestine: non-absorbable disaccharides interfere directly with the uptake of glutamine by the intestinal wall and its subsequent metabolism to ammonia (van Leeuwen *et al.* 1988).

Recently Kale *et al.* (2006) showed, using cerebral diffusion tensor imaging, that the interstitial brain oedema observed in patients with minimal hepatic encephalopathy resolves after 3 weeks treatment with lactulose in parallel with improvements in neuropsychiatric performance; it is unlikely, however, that this is a *direct* effect of treatment (Fig. 2).

Lactulose is generally prescribed as a syrup. The dose is adjusted to ensure passage of two semi-soft stools/day; typical doses range from 15 to 30 ml bd–qds. Approximately 30% of patients developing an aversion to its taste and may develop anorexia, flatulence and abdominal discomfort in the early weeks of treatment; however tolerance tends to improve over time. Improvements in neuropsychiatric status are observed in 67–87% of patients with hepatic encephalopathy, treated acutely, although removal of precipitating factors, if identifiable, can confound the interpretation of these results. Much less information is available on the efficacy of lactulose in the longer-term; compliance with treatment is a potential issue.

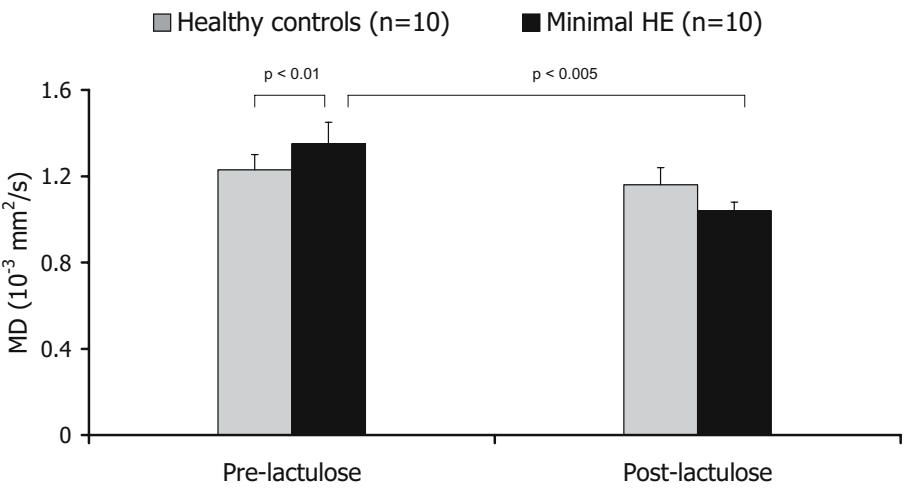

Fig. 2 Mean diffusivity (*MD*) in the corpus callosum measured using cerebral diffusion tensor imaging in ten healthy volunteers and in ten patients with cirrhosis and minimal hepatic encephalopathy before and after 3 weeks treatment with lactulose. The mean diffusivity is an index of water movement across the brain. Before treatment the patients had a significantly increased mean diffusivity, compared to the healthy controls, indicating the presence of interstitial brain oedema. After 3 weeks treatment with lactulose there was a significant reduction in the mean diffusivity to values comparable to the healthy controls. Parallel improvements were observed in psychometric test results (adapted from Kale *et al.* 2006)

Lactulose is also effective when delivered rectally (250 ml lactulose in 750 ml water; Uribe *et al.* 1987).

Lactitol is dispensed as a pure crystalline powder, which is extremely well tolerated. It is as efficacious if not more efficacious than lactulose (Morgan and Hawley 1987; Morgan *et al.* 1989). The doses required to ensure passage of two semi-soft stools/day range from 10 to 90 g. There is no equivalence between the effective doses of lactulose and lactitol.

Despite the fact that the non-absorbable disaccharides are used widely as first line therapy for hepatic encephalopathy, Als-Nielsen *et al.* (2004a) concluded, in their systematic review, that 'there is insufficient evidence at present to recommend or refute the use of non-absorbable disaccharides for hepatic encephalopathy' and that 'in consequence they should not be used as standard therapy in new therapeutic trials until they have been shown to confer benefit over placebo'.

These authors identified ten studies in which the efficacy of the non-absorbable disaccharides was compared with either no intervention or placebo. Overall there was a modest treatment effect (Relative Risk [RR] of no improvement 0.62 [95% CI 0.46–0.84]), but no effect on mortality. In the two studies deemed to be of 'high quality' which, nevertheless, included only 44 patients, there was no beneficial effect of treatment (RR 0.92 [CI 0.42–2.04]). In the remaining four studies, which were deemed to be of 'low-quality' but which included 163 patients, the majority with minimal hepatic encephalopathy, there was a significant treatment effect (RR 0.57 [CI 0.40–0.83]).

These authors also identified and assessed 12 trials comparing the efficacy of non-absorbable disaccharides with antibiotics for the treatment of hepatic encephalopathy,

which had a total enrolled population of 698 patients. Compared with antibiotics, patients taking a non-absorbable antibiotic had a significantly greater risk of 'no improvement of hepatic encephalopathy' (RR 1.24 [CI 1.02–1.50]).

Despite its authoritative credentials this review can be criticized on a number of counts not necessarily obvious without reference to the full review (Als-Nielsen *et al.* 2004b). (1) A large number of trials were not 'discovered ' during the literature search; (2) 134 of the 'discovered' studies were excluded as irrelevant; many should have been included; (3) 64 of the 108 'relevant discovered' studies were later excluded; many should have been retained; (4) the assessment of the included trials was poor; methodological quality was determined using only three criteria, viz generation of allocation sequence, allocation concealment and blinding; (5) very little attempt was made to differentiate findings in relation to the type of hepatic encephalopathy; (6) no attempt was made to unify outcomes; and (7) the end point 'number without improvement' was ill-judged.

Nevertheless, this systematic review, although not optimal, did raise the issue of the efficacy of the non-absorbable disaccharides as treatment for hepatic encephalopathy and their role as 'standard' treatment in other therapeutic trials. Thus, although many physicians are convinced, through long and successful use, that these agents are effective (Córdoba *et al.* 2005) others are more sceptical and have emphasized the need for placebo-controlled trials (Shawcross and Jalan 2005). Some workers have already risen to this challenge. Prasad *et al.* (2007), for example, have recently shown, in a placebo-controlled trial, that lactulose significantly improves both cognitive function and health-related quality of life in patients with minimal hepatic encephalopathy. Further studies are underway.

Antibiotic therapy

Neomycin, a poorly absorbed amino-glycoside antibiotic, was the standard, and indeed, the only treatment available for hepatic encephalopathy from 1957 until the introduction of lactulose in 1966. Its beneficial effect relates to its ability to eliminate urease-producing organisms from the intestinal tract, thereby reducing the production of ammonia. However, plasma concentrations of up to 7.2 μg/ml have been reported in patient with cirrhosis following a 4 g oral dose (Kunin *et al.* 1960); this may result in nephrotoxicity which has been reported in 8% of patients treated for more than a few weeks, and of irreversible ototoxicity in a slightly lower percentage.

Although neomycin was considered to be efficacious as a treatment for hepatic encephalopathy there was very little evidence to support its use. Indeed two randomized, placebo-controlled trials undertaken in the 1990s failed to show any significant effect of neomycin, given either alone or with lactulose, in the treatment of acute hepatic encephalopathy in patients with cirrhosis (Strauss *et al*. 1992; Blanc *et al.* 1994).

Rifaximin, a synthetic antibiotic structurally related to rifamycin, has a very low rate of systemic absorption (0.4%). Its use as a first line therapy for hepatic encephalopathy in several countries in Europe, Asia, Africa and Latin America is supported by numerous published studies designed to assess its efficacy and safety, although most comparisons were undertaken against other medications rather than

placebo. In 15 studies, several of which were adequately powered, rifaximin was at least as effective as lactulose/lactitol and other non-absorbable antibiotics for example neomycin and paromomycin, for the treatment of hepatic encephalopathy (Bass 2006).

Both rifaximin and non-absorbable disaccharides reduce blood ammonia levels and improve neuropsychiatric symptoms. However, rifaximin is associated with earlier, more marked improvements in neuropsychiatric status and is better tolerated than the non-absorbable disaccharides. Mas *et al.* (2003), for example, undertook a randomized, double-blind, double-dummy study of rifaximin 1,200 mg/day (n=50) and lactitol 60 g/day (n=53) in patients with Grade I–III hepatic encephalopathy. Treatment was administered for 5–10 days. Improvements in neurological parameters and blood ammonia concentrations were observed in both treatment groups. Comparable percentages of patients showed clinical improvement at the end of the treatment period (rifaximin 82%: lactitol 80%). However, the improvements in blood ammonia concentrations and in the hepatic encephalopathy index were significantly greater in the rifaximin-treated patients, as were the number of patients who showed complete resolution of their neuropsychiatric abnormalities.

Rifaximin has also been shown to be either equally or more efficacious than other antibiotics but is invariably better tolerated. Pedretti *et al.* (1991), for example, undertook a randomized, double-blind comparison of rifaximin 1,200 mg/day (n=15) and neomycin 3 g/day (n=15) in patients with Grade I–III hepatic encephalopathy. Patients were treated for 21 days. Significant improvements were observed in neuropsychiatric status and blood ammonia concentrations in both treatment group, but the improvements in psychometric performance and blood ammonia concentrations were significantly greater in the patients treated with rifaximin. Blood urea nitrogen and plasma creatinine levels increased in 26% of the patients receiving neomycin and 33% reported nausea, abdominal pain and vomiting; none of the rifaximin-treated patients experienced adverse events.

This agent has been approved for the prophylaxis of traveler's diarrhoea in the United States of America. A large multicentre trial of rifaximin plus lactulose versus placebo plus lactulose in patient with a history of at least two episodes of hepatic encephalopathy is currently underway; the primary end point is the time to the next episode of documented encephalopathy.

Rifaximin has an excellent safety profile and hence the highest benefit–risk ratio of all treatments for this condition. In addition, in the countries in which it is licensed for this indication, it is extremely competitively priced and has proven cost-effectiveness.

Leevy and Phillips (2007), undertook a single-centre, retrospective chart review comparing the frequency of hospitalizations and associated outcomes in 145 patients with hepatic encephalopathy treated initially with lactulose 60 ml/day for 6 months or more and then with rifaximin 1,200 mg/day for 6 months or more. Compliance during the rifaximin period was significantly better; 92% of the patients reported taking at least 75% of the prescribed medication, compared with only 31% during the lactulose period; the incidence of side-effects was also lower during the rifaximin period. Overall, rifaximin was significantly more effective than lactulose, related perhaps in part to the issues of compliance and side-effects. Thus, during the rifaximin period there were fewer hospitalization (0.5 *cf.*1.6; $p<0.001$); fewer days spent in hospital (2.5 *cf.* 7.3; $p<0.001$); fewer weeks spent in hospital (0.4 *cf.*1.8; $p<$

0.001) and, overall, four times lower hospitalization charges per patient ($14, 222 cf. $56, 635).

Neff *et al.* (2006), reviewed the medical records of 39 liver transplant candidates who presented with Grade II hepatic encephalopathy and were subsequently treated with either lactulose (n=24) or rifaximin (n=15). During the follow-up period, 19 patients treated with lactulose but only three treated with rifaximin required admission. The average length of stay was longer in the patients treated with lactulose (5.0 days [range 3–10] *cf.* 3.5 days [range 3–4]; $p<0.0001$). Treatment with lactulose cost $50 dollars/month while treatment with rifaximin cost $620 dollars/month. The total cost of therapy including drug costs, emergency room visits and hospital care for the patients treated with lactulose, was $13,285/patient/year, while the total cost of therapy for the patients treated with rifaximin was significantly lower at $7,958/patient/year. However, data generated from prospective studies are needed to confirm the cost-effectiveness of this treatment.

One of the major risks associated with the long-term use of even non-absorbable antibiotics is the emergence of multiresistant organisms. One solution might be to use rifaximin intermittently with perhaps the addition of probiotics during the 'off-treatment' periods (Lighthouse *et al.* 2004).

Branched-chain amino acids

Branched-chain amino acid (BCAA) supplements have been used to treat hepatic encephalopathy for at least 25 years although no new or additional data have been published in the last 15 years. A number of systematic reviews and meta-analyses have been performed to data, the most recent being a comprehensive Cochrane review on the use of intravenous and oral BCAA for hepatic encephalopathy (Als-Nielsen *et al.* 2004c). The authors of this review concluded that patients receiving BCAA are more likely to recover from hepatic encephalopathy than patients treated with a variety of control regimens, including carbohydrates, neomycin/lactulose, or isonitrogenous diets (59 vs 41%; RR, 1.31 [CI 1.04–1.66]), but there was no convincing evidence for an effect of BCAA on survival. The authors remarked that the majority of studies involved only small numbers of patients, that follow-up periods were short, and that most trials were of low methodological quality (Als-Nielsen *et al.* 2004c). However, two large studies of BCAA supplementation published in recent years (Marchesini *et al.* 2003; Muto *et al.* 2005) have shown beneficial effects of BCAA on nutrition and progression free survival which may largely outweigh any beneficial effects on hepatic encephalopathy.

In a multicentre, randomized study, Marchesini *et al.* (2003), compared long-term BCAA supplementation with equicaloric (maltodextrine) or equicaloric/equinitrogenous supplements (lactoalbumin) in 174 patients with advanced cirrhosis. Treatment with BCAA significantly reduced the combined event rates (death or progression to liver failure) compared with lactoalbumin (hazard ratio, 0.43 [CI 0.19–0.96] p=0.039) and non-significantly compared with maltodextrins (odds ratio, 0.51 [CI 0.23–1.17] p=0.039), and reduced the need for hospital admission and duration of hospital stay. In patients who remained in the study, nutritional parameters and liver function tests were, on average, stable or improved during BCAA treatment, as did anorexia and health-related quality of life. In a Japanese study in 622 patients with cirrhosis,

long-term BCAA supplements significantly reduced the progression to liver failure or death (hazard ratio, 0.67 [CI 0.49–0.93] p=0.015) compared to diet alone, and tended to reduce the incidence rates of hepatic encephalopathy (0.6 vs 1.9%; p=0.10; Muto *et al.* 2005).

The mechanism of the beneficial effects of BCAA is unknown but there is evidence that it may stem from increased availability of substrates for protein synthesis in liver parenchyma. Leucine is a potent stimulator of the production of hepatocyte growth factor (HGF) by stellate cells (Tomiya *et al.* 2002); HGF is a pleiotropic substance with mitogenic activity (Ishiki *et al.* 1992). Accordingly, the prevention of liver failure observed in patients with advanced cirrhosis, during BCAA supplementation, might stem from increased liver regeneration, compensating for progressive liver cell death. Improvements in liver function might, in turn, have a beneficial effect, albeit indirectly, on hepatic encephalopathy. Recently, however, Yamamoto *et al.* (2005), provided evidence that BCAA might have a more direct effect on cerebral function. These authors measured regional cerebral blood flow, using single photon emission computed tomography, in 29 patients randomized to either oral BCAA or cornstarch, and showed a significant increase in cerebral perfusion, in several brain areas, within 70 min of BCAA ingestion, to values comparable to healthy controls; cornstarch had no effect. Similar effects had been demonstrated previously during BCAA infusion (Iwasa *et al.* 2003). No explanation for this effect of BCAA on cerebral blood flow was provided but it is most likely mediated through changes in cerebral metabolic rate.

L-Ornithine–L-Aspartate

Ornithine aspartate (OA) is the stable salt of the two amino acids L-ornithine and L-aspartate; it has been shown to have ammonia lowering properties. The ornithine moiety activates ornithine carbamoyl transferase and carbomyl phosphate synthetase and acts as a substrate for ureagenesis; the aspartate moiety enhances hepatic glutamine synthesis. A number of preliminary, uncontrolled studies were undertaken to assess the efficacy of OA in the treatment of hepatic encephalopathy in patients with cirrhosis in the 1970s but there was no evidence base for its use until the publication of several randomized, controlled trials in the last 10 years.

Intravenous infusion of OA will reduce elevated circulating ammonia levels in patient with cirrhosis (Kircheis *et al.* 1996) and will reduce, if not entirely prevent, the elevations in blood ammonia levels produced in these patients by intravenous ammonium chloride (Henglein-Ottermann 1976), oral glutamine (Rees *et al.* 2000), and protein ingestion (Staedt *et al.* 1993). The maximal recommended infusion dose is 5 g OA/h; higher infusion rates are associated with a significant incidence of adverse events such as nausea and vomiting (Kircheis *et al.* 1996).

The efficacy of intravenous OA in the treatment of hepatic encephalopathy has been examined in only two studies published to date. Leonhardt and Bungert (1972) undertook an open trial of treatment with 80–120 g OA daily for 2 days in 30 patients with cirrhosis, hyperammonaemia and manifest Grade II–III hepatic encephalopathy (Kalk 1958). Improvements in mental status were observed in 28 (94%) of the 30 patients within the first 6 h of treatment, with concomitant

reductions in the mean arterial ammonia concentrations. This trial has been criticized because it was uncontrolled and because few, if any, details were provided of the other measures instigated to support the patients. Subsequently, a number of randomized controlled trials were undertaken to assess the efficacy of intravenous OA in patients with hepatic encephalopathy but, with one exception (Kircheis *et al.* 1997), these remain unpublished. In the study by Kircheis *et al.* (1997), 126 patients with cirrhosis and either minimal or manifest low-grade hepatic encephalopathy were randomized to treatment with either intravenously OA, 20 g/day infused over 4 h, or to a placebo infusion, for 7 days. Overall improvements in mental state, blood ammonia concentrations and psychometric test performance were seen in significantly more patients receiving OA than placebo (59 *cf.* 32%; $p<0.001$). These improvements were almost invariably confined to those patients with manifest rather than minimal hepatic encephalopathy.

The efficacy of oral OA for the treatment of hepatic encephalopathy has been evaluated in three published studies to date. Stauch *et al.* (1998) randomized 63 patients with cirrhosis and varying degrees of hepatic encephalopathy to treatment with OA 6 g three times a day, or to a placebo, for 14 days. Following treatment there was no significant difference in mental state between the two groups although significantly more patients receiving OA showed improvement in performance of Number Connection Test A and reductions in fasting and postprandial venous blood ammonia levels. These improvements were, however, exclusive to patients with Grade II hepatic encephalopathy; treatment had no effect in patients with minimal or Grade I hepatic encephalopathy. A much larger, similarly designed trial, in which 192 patients were randomized to treatment with OA or placebo for 6 week, confirmed these findings, but has only been published in abstract form (Fleig *et al.* 1999). More recently Poo *et al.* (2006) undertook a very small study in which 20 patients with cirrhosis and overt hepatic encephalopathy were randomized to treatment with either lactulose or OA for 2 weeks; they found that while both agents reduce circulating ammonia levels, use of OA was also associated with significant improvements in mental status, psychometric parameters and EEG activity.

It is difficult to comment on the efficacy of OA in the treatment of hepatic encephalopathy based on the studies available to date. A number of other studies have been completed but remain unpublished in the Company archives. From the data that are available it would appear that OA is most effective when given by intravenous infusion to patients with severe hepatic encephalopathy. This may reflect the fact that when given by this route both the ornithine and aspartate moieties are available for ‘ammonia fixation’ whereas following oral administration most of the aspartate undergoes transamination in the intestinal mucosa so that the efficacy of OA when given by this route is largely dependent on the effects of the ornithine moiety alone. The situation may not, however, be as simple as this as the fate of the glutamine generated from the ornithine in muscle is still unclear (Jalan *et al.* 2007).

Zinc

Zinc is an essential trace element and is a component of many metalloenzymes and metal-protein complexes such as metallothionine. It plays an important role in the

regulation of protein metabolism and membrane integrity and in immune responsiveness. A number of abnormalities have been reported in patients with chronic liver disease, which might reflect the presence of zinc deficiency, for example, photoreceptor dysfunction, abnormalities of taste and smell, hypogonadism and immune dysfunction. Poor zinc status impairs nitrogen metabolism by reducing the activity of urea cycle enzymes in the liver (Rabbani and Prasad 1978; Riggio *et al.* 1992) and of glutamine synthetase in muscle (Prasad *et al.* 1978; Yoshida *et al.* 2001). Zinc deficiency is, therefore, associated with altered nitrogen metabolism, both in experimental models of cirrhosis in the rat (Riggio *et al.* 1992) and in patients with advanced liver disease (Marchesini *et al.* 1996). It has also been postulated that zinc deficiency may play a role in the pathogenesis of hepatic encephalopathy as serum zinc concentrations are reduced in patients with this condition and correlate inversely with blood ammonia concentrations (Reding *et al.* 1984; Grüngreiff *et al.* 1989). This postulate is supported by the observations made by Van der Rijt *et al.* (1991) of a patient with severe recurrent hepatic encephalopathy and zinc deficiency. Long-term zinc supplementation improved the patient's encephalopathy and quality of life.

A small number of controlled studies have been undertaken, to date, to examine the efficacy of zinc in the treatment of hepatic encephalopathy in patents with cirrhosis. The results are conflicting. The studies vary widely in the types and doses of zinc preparations used and in the duration of therapy (Table 1). Three report a significant improvement in mental state (Marchesini *et al.* 1996; Reding *et al.* 1984; Schölmerich 1987). Reding *et al.* (1984) performed a double-blind, randomized, placebo-controlled trial of zinc acetate, in a dose of 600 mg/day for 7 days and demonstrated improvement in mental state, increased serum zinc levels, and slightly increased blood urea nitrogen. This study has, however, been criticised because the patients were also protein restricted and received lactulose. In a randomized trial comparing zinc sulphate or zinc histidine to placebo, Schölmerich (1987) found an improvement in hepatic encephalopathy grade, dark adaptation, and an increase in the zinc content of the hair after 3 months of treatment. Marchesini *et al.* (1996) described normalization of the zinc levels, an increase of the hepatic nitrogen clearance by 25%, and an improvement in psychometric tests after 3 months supplementation with 600 mg zinc sulphate daily in patients with advanced cirrhosis. However, a more detailed study by Riggio *et al.* (1991), using the same dose of zinc sulphate, for ten days, failed to demonstrate any benefit from zinc therapy. Rössle *et al.* (1997), also reported negative results. These workers investigated the effect of 100 mg zinc hydrogen-aspartate daily for 3 months in 42 patients following TIPSS insertion. They found an increase in circulating zinc concentrations and a significant reduction in blood ammonia concentrations but no improvement in mental status. Grüngreiff *et al.* (2000), observed a decrease in plasma ammonia levels and an improvement in the grade of hepatic encephalopathy in about 55–60% of 34 patients who had been treated for 6–42 months with either oral zinc hydrogen aspartate 100 mg/day or zinc histidine 45 mg/day in combination with OA. Withdrawal of the zinc supplementation resulted in a reduction in circulating zinc levels and an increase in plasma ammonia levels. A synergistic effect of zinc with BCAA and lactulose has also been observed (Katayama 2004).

The studies undertaken, to date, do not provide clear evidence of a beneficial effect for zinc supplementation in patients with hepatic encephalopathy. Further

Table 1 Clinical trials of zinc supplementation in the treatment of hepatic encephalopathy

Author and date	Study design	Duration	Patients (*n*)	Treatment
Reding *et al.* (1984)	Randomized; placebo-controlled	7 days	22	Zn acetate 600 mg/day
Schölmerich (1987)	Randomized; placebo-controlled	3 months	12 12	Zn sulphate 135 mg /day Zn histidine 45 mg/day
Riggio *et al.* (1991)	Randomized; placebo controlled; cross-over	10 days	15	Zn sulphate 600 mg/day
Marchesini *et al.* (1996)	Open; controlled	3 months	16	Zn sulphate 600 mg/day
Rössle *et al.* (1997)	Open; controlled	3 months	42	Zn hydrogen aspartate 100 mg/day

there are questions about the long-term safety of zinc supplementation, which will need to be resolved (Chandra and McBean 1994; Prasad *et al.* 1978).

Other therapies

Bromocriptine Patients with stable, chronic, persistent hepatic encephalopathy, but otherwise well-compensated cirrhosis, may benefit significantly from treatment with the dopamine agonist bromocriptine (Morgan *et al.* 1980). The dose is gradually increased from 2.5 mg o.d. to a maximum of 5 mg b.d. Ototoxicity has been reported (Lanthier *et al.* 1984), and treated patients should be carefully monitored with audiograms 6-monthly; treatment should be reserved for patients with well-compensated liver disease as use in patients with ascites has been associated with the syndrome of inappropriate ADH secretion (Marshall *et al.* 1982).

Sodium benzoate This compound is used to treat individuals with urea cycle enzyme deficiencies because it metabolically fixes ammonia by utilizing alternative pathways for waste nitrogen excretion; it conjugates with glycine and the excess nitrogen is excreted in the urine as hippurate. In the one large, randomized, controlled trial available to date, this compound was equally as efficacious as lactulose for the treatment of hepatic encephalopathy but possibly less well tolerated (Sushma *et al.* 1992). The daily recommended dose is 5 g b.d. but the benzoate is dispensed in bulky 500 mg capsules and patients rarely tolerate more than 2 g b.d., not only because of the tablet load, but also its gastro-intestinal side-effects.

Probiotics Urease-producing bacteria catalyze the hydrolysis of urea to carbamate and ammonia and exist in abundance in the human gut. Patients with cirrhosis appear to harbour more urease-productive bacteria than healthy individuals (Lai *et al.* 1972), which results in increased production of nitrogenous compounds, particularly ammonia. Altering the gut flora by introducing bacteria, which compete with the urease-producing bacteria, so-called probiotics, can decrease the amount of ammonia in the portal blood. The studies undertaken to date have employed either *Lactobacillus acidophilus* or *Enterococcus faecium SF68* and have shown some benefit (Macbeth

et al. 1965; Loguercio *et al.* 1995; Liu *et al.* 2004). The use of highly concentrated combination probiotics, which have additional beneficial effects, such as lowering circulating cytokine levels, may be more effective for the treatment of hepatic encephalopathy (Loguercio *et al.* 2005).

Potential therapies

The treatment of hepatic encephalopathy is currently based on strategies aimed at reducing the production and absorption of ammonia from the colon. However, other sites, for example, the small intestine, kidney and muscle, are also involved in the metabolism of ammonia and may provide targets for future therapy (Fig. 1).

The small intestine is an important source of ammonia generation through the uptake and breakdown of glutamine by enterocytes (Olde Damink *et al.* 2002). Non-absorbable disaccharides are known to interfere directly with the uptake of glutamine by the intestinal wall and its subsequent metabolism (van Leeuwen *et al.* 1988). Phosphate-activated glutaminase (PAG) is the main glutamine-catabolizing enzyme in the small intestine. Duodenal PAG activity is nearly four times higher in patients with cirrhosis than in healthy controls (Romero-Gómez *et al.* 2004); the major factors regulating intestinal ammonia production in cirrhotics via PAG are portal hypertension and systemic inflammation. Inhibiting PAG activity in the small intestine might reduce circulating blood ammonia levels with therapeutic benefit.

The kidneys both produce and excrete ammonia (Dejong *et al.* 1993). In patients with cirrhosis plasma expansion results in a significantly increase in renal ammonia excretion and a consequent reduction in plasma ammonia concentrations. This indicates that the kidneys can be manipulated to facilitate ammonia excretion (Jalan and Kapoor 2004).

Ammonia can be detoxified in muscle, when circulating ammonia levels are high, through conversion to glutamine (Olde Damink *et al.* 2003). This pathway for lowering circulating ammonia levels could be exploited further—for example administration of OA provides intermediates and increases substrate availability for this process.

In addition a number of other potentially important pathogenic mechanisms have been identified, in recent years, which suggest possible alternative treatment approaches in man.

L-carnitine is used therapeutically to treatment hyperammonaemia in children with urea-cycle enzyme deficiencies (Matsuda *et al.* 1987) and valproate-induced hyperammonaemia (Raskind and El-Chaar 2000). The protective effects of L-carnitine are centrally mediated by activation of metabotropic Glu receptors at the level of brain ammonia uptake and/or mitochondrial energy metabolism. Preliminary studies have been undertaken in patients with hepatic encephalopathy but have not been monitored objectively (Malaguarnera *et al.* 2005).

Endocarbinoids Neural intoxication in hepatic encephalopathy disrupts cerebral energy flux; therapy should, therefore, aim at strengthening energy defence

mechanisms. AMP-activated protein kinase (AMPK) rehabilitates cellular energy stores in response to metabolic injury; its activity can be augmented by cannabinoid compounds. Animal studies have confirmed that pharmacological activation of AMPK by endocarbinoids confers neuroprotection in hepatic encephalopathy (Dragon *et al.* 2007).

Sildenafil Alterations in the function of the glutamate-nitric oxide-cGMP pathway and the subsequent decrease in extracellular cGMP in brain may be responsible for the impairment in learning ability and intellectual function in patients with hepatic encephalopathy. Pharmacological modulation of extracellular cGMP concentration using sildenafil, an inhibitor of the phosphodiesterase, which crosses the blood-brain barrier, restores learning ability in animal models (Erceg *et al.* 2005).

mGluR1 antagonists Alterations in glutamatergic neurotransmission in the substantia nigra pars reticulata may contribute to the psychomotor slowing and hypokinesia observed in patients with hepatic encephalopathy. Blocking mGluR1 at this site normalizes motor activity in a rat model of hepatic encephalopathy (Canales *et al.* 2003).

Systemic inflammation Recent interest has focused on the potential role of inflammatory mediators in the pathogenesis of hepatic encephalopathy (Blei 2004; Shawcross *et al.* 2004, 2007). Modulation of the systemic inflammatory response with, for example, anti-inflammatory agents should be explored with the obvious caveats governing the use of these agents in patients with cirrhosis.

Finally a symptom-related approach should be considered for some of the more distinct clinical symptoms associated with hepatic encephalopathy such as sleep disturbances, extrapyramidal symptoms, mood disturbances and cognitive decline.

Conduct of future trials

Few, if any of the agents used to treat hepatic encephalopathy, at the present time, have been subject to rigorous evaluation by way of placebo-controlled trials. Many

Table 2 Hospital costs for the drugs used to treat hepatic encephalopathy, in the UK

Drug	Dosage	Cost/month[b]		
Lactulose[a]	30 ml tds (maximum)	£ 13	€ 19	$ 25
Lactitol	20 g tds (average)	£ 118	€ 174	$ 235
Neomycin[a]	1 g qds (maximum 1 week)	£ 36	€ 53	$ 71
Rifaximin	400 mg tds	£ 181	€ 267	$ 359
Sodium benzoate	5 g bd	£ 288	€ 424	$ 570
Bromocriptine	5 mg bd	£ 17	€ 25	$ 33
L-ornithine L-aspartate	6 g tds	£ 139	€ 204	$ 275

[a] Drugs licensed for this indication in the UK
[b] Includes VAT at 17.5%

of these 'established' therapies need to be revisited and several new potential treatments need to be evaluated. A number of considerations need to be taken into account in the conduct of these future trials:

1. It has been argued that therapeutic trials in patients with hepatic encephalopathy should always be placebo-controlled. This would certainly be possible, ethically allowable and desirable in patients (1) with minimal hepatic encephalopathy and/or low grade manifest encephalopathy (Grade I) and (2) patients with stable, persistent Grade II encephalopathy. At present it would be difficult to ethically justify placebo-controlled trials in patients with advanced liver disease with precipitated bouts of hepatic encephalopathy unless the treatment under trial were expected, perhaps as a result of a previous open or proof of concept study, to produce rapid and discernable effects. This point will, however, continue to be debated.
2. Improvement in neuropsychiatric status can be observed in 20–40% of patients with hepatic encephalopathy following institution of general supportive measures. Allowance must be made for this in power calculations.
3. Therapies that are effective in one clinical situation may not translate directly into other situations. Thus, care must be taken not to extrapolate the findings from trials in patients in minimal hepatic encephalopathy directly to patients with manifest symptoms of this syndrome.
4. Therapeutic agents are not universally licensed for use. This has a considerable effect on pricing and hence the ability of physicians to prescribe drugs, even those of proven or superior efficacy. This should be taken into account in the design of trials. In the United Kingdom, at present, the only drugs licensed for use in hepatic encephalopathy are lactulose and neomycin. Other agents can be prescribed on a named patient basis but at considerable cost (Table 2). Thus, all new therapeutic trials should include an analysis of the cost-benefits and cost-effectiveness of treatments with details of how these factors might be affected by current licensing arrangements.

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