Complications of cirrhosis

III. Hepatic encephalopathy

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Hepatic encephalopathy (HE) is a major neuropsychiatric complication of cirrhosis. HE develops slowly in cirrhotic patients, starting with altered sleep patterns and eventually progressing through asterixis to stupor and coma. Precipitating factors are common and include an oral protein load, gastrointestinal bleeding and the use of sedatives. HE is common following transjugular intrahepatic portosystemic stent shunts (TIPS). Neuropathologically, HE in cirrhotic patients is characterized by astrocytic (rather than neuronal) changes known as Alzheimer type II astrocytosis and in altered expression of key astrocytic proteins. Magnetic resonance imaging in cirrhotic patients reveals bilateral signal hyperintensities particularly in globus pallidus on T1-weighted imaging, a phenomenon which may result from manganese deposition. Proton (1H) magnetic resonance spectroscopy shows increases in the glutamine resonance in brain, a finding which confirms previous biochemical studies and results no doubt from increased brain ammonia removal (glutamine synthesis). Additional evidence for increased brain ammonia uptake and removal in cirrhotic patients is provided by studies using positron emission tomography and 13NH3. Recent molecular biological studies demonstrate increased expression of genes coding for neurotransmitter-related proteins in chronic liver failure. Such genes include monoamine oxidase (MAO-A isoform), the peripheral-type benzodiazepine receptor and nitric oxide synthase (nNOS isoform). Activation of these systems has the potential to lead to alterations of monoamine and amino acid neurotransmitter function as well as modified cerebral perfusion in chronic liver failure. Prevention and treatment of HE in cirrhotic patients continues to rely on ammonia-lowering strategies which include assessment of dietary protein intake and the use of lactulose, neomycin, sodium benzoate and L-ornithine-aspartate. The benzodiazepine receptor antagonist flumazenil may be effective in certain cases. A more widespread use of central nervous system-acting drugs awaits a more complete understanding of the precise neurotransmitter systems involved in the pathogenesis of HE in chronic liver failure.

Key words: Ammonia; Chronic liver failure; Cirrhosis; Hepatic encephalopathy; Magnetic resonance imaging; Manganese; Monoamine oxidase; Nitric oxide synthase; Peripheral-type benzodiazepine receptors; Portal-systemic encephalopathy; Positron emission tomography; Serotonin; TIPS.
In “subclinical” hepatic encephalopathy, patients may have a normal neurological status on standard clinical evaluation but manifest neuropsychological deficits involving both cognitive and motor performance skills. The prevalence of subclinical hepatic encephalopathy as defined by deficits in psychometric test scores in cirrhotic patients may be as high as 84% (1). Psychometric tests routinely used for the diagnosis and assessment of subclinical hepatic encephalopathy include the Number Connection Test, the Block Design Test, the Digit Symbol Test and Reaction Times to Sound or Light stimuli. Further details of these tests and their uses and possible pitfalls are described in a recent review article (1). Psychometric tests are more sensitive than electrophysiological measurements based upon stimulus-evoked potentials in patients with subclinical hepatic encephalopathy. However, electrophysiological tests may be more specific, so that a combination of the two approaches could be advantageous.

Subclinical hepatic encephalopathy impacts negatively on the quality of life in cirrhotic patients, particularly with regard to their quality of sleep and rest (2).

Post-TIPS encephalopathy
The TIPS procedure is a non-surgical intervention that is used for the treatment of portal hypertension and often results in an effective means of prevention of variceal bleeding and in the treatment of ascites. However, the TIPS procedure results in new or worsening episodes of HE in a large percentage of cirrhotic patients as shown in Table 1 (3–11).

Post-TIPS encephalopathy is characterized by the occurrence of spontaneous episodes of HE, by the occurrence of chronic HE in 10–20% of patients and by improvement in neurological status during follow-up (5). This improvement most likely relates to a progressive stenosis of the shunt over time as well as to metabolic adaptation to the hemodynamic changes caused by TIPS (3).

Predictors of post-TIPS encephalopathy include (i) the presence of encephalopathy prior to the TIPS procedure, (ii) a non-alcoholic etiology of cirrhosis, (iii) hypoalbuminemia and (iv) the age of the patient. The consistent observation of increased incidence of post-TIPS encephalopathy in older cirrhotic patients may relate to the increased sensitivity of brain to liver-gut-derived neurotoxins such as ammonia (12).

**Neuropathology of HE in chronic liver failure**
HE in chronic liver failure is characterized neuropathologically by alterations of astrocyte morphology and function; no consistent histological changes to neurons have been described in the brain in chronic liver disease. It has therefore been proposed that HE represents the first example of a primary “astrocytopathy” or “gliopathy” (13). The morphological changes that characterize HE are collectively known as Alzheimer Type II astrocytosis, a typical example of which is shown in Fig. 1.

Alzheimer Type II astrocytes exhibit large swollen nuclei with margination of the chromatin pattern, resulting in a large pale nucleus and prominent nucleolus. These astrocytic changes are seen throughout the brains of patients with end-stage chronic liver failure (14) in both grey and white matter structures.

Astrocytes are the only cells in the mammalian brain to contain the necessary metabolic machinery (glutamine synthetase) for ammonia removal since brain is devoid of an effective urea cycle. It is therefore the astrocyte that bears the brunt of ammonia removal in brain and the astrocyte that ultimately shows the most consistent morphological changes. Astrocytes in chronic liver failure also manifest alterations in expression of many key proteins, as discussed in a subsequent section of this review.

**TABLE 1**
Incidence of hepatic encephalopathy (HE) after transjugular intrahepatic portosystemic stent shunt (TIPS)

<table>
<thead>
<tr>
<th>Study (Reference)</th>
<th>n</th>
<th>Pugh Class (%)</th>
<th>New or worsened HE (%)</th>
<th>Chronic HE (%)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>A</td>
<td>B</td>
<td>C</td>
</tr>
<tr>
<td>Somberg et al., 1995 (4)</td>
<td>77</td>
<td>16</td>
<td>55</td>
<td>29</td>
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<tr>
<td>Sanyal et al., 1994 (5)</td>
<td>80</td>
<td>20</td>
<td>35</td>
<td>47</td>
</tr>
<tr>
<td>Dagenais et al., 1994 (6)</td>
<td>45</td>
<td>2</td>
<td>51</td>
<td>47</td>
</tr>
<tr>
<td>Coldwell et al., 1995 (7)</td>
<td>96</td>
<td>25</td>
<td>40</td>
<td>35</td>
</tr>
<tr>
<td>Rössle et al., 1994 (8)</td>
<td>100</td>
<td>27</td>
<td>52</td>
<td>22</td>
</tr>
<tr>
<td>Martin et al., 1993 (9)</td>
<td>45</td>
<td>22</td>
<td>58</td>
<td>20</td>
</tr>
<tr>
<td>Ochs et al., 1995 (10)</td>
<td>50</td>
<td>36</td>
<td>64</td>
<td>44</td>
</tr>
<tr>
<td>Jalan et al., 1995 (11)</td>
<td>68</td>
<td>25</td>
<td>4</td>
<td>31</td>
</tr>
</tbody>
</table>

Adapted from Pomier Layrargues, 1996 (ref. 3)
Non-invasive techniques for the study of HE

Non-invasive techniques such as magnetic resonance imaging and spectroscopy as well as positron emission tomography are increasingly being used for the study of the central nervous system consequences of chronic liver failure (15).

Magnetic resonance imaging (MRI)

The most consistent finding on MRI of cirrhotic patients is bilateral, symmetrical hyperintensities in globus pallidus on T1-weighted imaging. A typical example of these signal hyperintensities is shown in Fig. 2.

The cause of these pallidal signal hyperintensities as well as their relationship to the extent of liver damage, the presence of portal-systemic shunting and to the clinical neuropsychiatric status of the patient have been the subject of several investigations. However, little (if any) consensus has emerged (16–18). On the other hand, it is clear that the pallidal signal hyperintensities on MRI of patients with end-stage liver failure are reversible, since successful liver transplantation results in their disappearance (19).

As to the cause of these signal hyperintensities, most evidence available at the present time points to a role of manganese deposition. Manganese is a neurotoxic metal whose elimination takes place via the hepatobiliary route. Blood manganese concentrations are increased in cirrhotic patients who manifest pallidal signal hyperintensities on MRI (18). Furthermore, similar pallidal signal hyperintensities have been described in a patient with Alagille's Syndrome, a hereditary disorder characterized by cholestasis, intrahepatic bile duct paucity and increased blood manganese (20). Pallidal MRI signal hyperintensities have also been described in patients during total parenteral nutrition where it was again proposed that the cause was manganese accumulation in the brain (21). Histopathological evaluation of pallidal tissue from cirrhotic patients who had manifested pallidal signal hyperintensities on MRI during life reveals Alzheimer Type II astrocytosis (16), suggesting that the astrocytic pathology characteristic of HE in chronic liver failure may be caused, at least in part, by manganese accumulation.

The most convincing evidence for manganese as the causal agent in the pallidal signal hyperintensities observed in cirrhotic patients comes from direct studies of manganese content of dissected pallidal tissue obtained at autopsy from cirrhotic patients (Table 2). In contrast to other metals, including copper and zinc, manganese concentrations were found to be increased up to 7-fold in pallidal samples from these patients (22,23). More recent studies in experimental animals with surgical portacaval shunts or experimental biliary cirrhosis revealed selective accumulation of manganese in pallidum (Table 2) (and to a lesser extent in other basal ganglia structures), suggesting that both portal-systemic shunting and impaired hepatobiliary elimination may be implicated in brain manganese accumulation in chronic liver failure (24).
TABLE 2

Brain manganese concentrations in dissected pallidal tissue from cirrhotic patients who died in hepatic coma and from rats with experimental acute or chronic liver failure

<table>
<thead>
<tr>
<th>Patients</th>
<th>Pallidal manganese concentrations (µg/g)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Controls (n)</td>
</tr>
<tr>
<td></td>
<td>Cirrhotics (n)</td>
</tr>
<tr>
<td>Rats</td>
<td>Controls (Sham-operated) (n)</td>
</tr>
<tr>
<td></td>
<td>Portocaval-shunted (n)</td>
</tr>
<tr>
<td></td>
<td>Bile-duct ligated (cirrhosis) (n)</td>
</tr>
<tr>
<td></td>
<td>Hepatic devascularization (acute liver failure) (n)</td>
</tr>
</tbody>
</table>

Values represent mean±SE of determinations in dissected pallidal tissue. n=number of samples. Values significantly different from the appropriate control group indicated by *p<0.05, **p<0.01 (23,24).

Data from ref. 24.

Magnetic Resonance Spectroscopy (MRS)

'\(^1\)H\) (proton) MRS is currently being used as a research tool to measure brain metabolites in cirrhotic patients with HE (25,26). Studies using sufficiently high magnetic field strengths reveal increases in resonances assigned to the protons of the glutamine molecule (26). Increases of brain glutamine no doubt result from increased removal of ammonia via glutamine synthesis in the brain. In addition to increases in the glutamine resonances, reductions in resonances assigned to the protons of myoinositol have consistently been reported in the brains of cirrhotic patients using the \(^1\)H-MRS procedure (27) and it has been suggested that these changes reflect disturbances in cell volume regulation in the brain in chronic liver failure. Studies using lower field strengths yield information in the form of metabolite ratios which, although possibly useful as a "fingerprint" for the diagnosis of HE, are of limited value in the study of pathophysiologic mechanisms.

\(^31\)P (phosphorus) MRS yields seven major resonances, three of which have been assigned to the \(\alpha\), \(\beta\) and \(\gamma\) phosphate groups of the ATP molecule. Consequently, this technique has been used to study brain energy status in the brains of cirrhotic patients with varying degrees of severity of HE. To date, no convincing evidence of alterations of ATP, phosphocreatine or ATP/phosphocreatine ratios has been observed in these patients (28). Furthermore, \(^31\)P-MRS studies performed in pallidum of cirrhotic patients who manifest MRI signal hyperintensities did not show any significant alterations of \(^31\)P resonances (29), suggesting that manganese deposition in the brains of these patients does not result in local cerebral energy failure.

Postiron emission tomography (PET)

Using the PET ligand \(^18\)F-fluorodeoxyglucose, several reports have described alterations of local cerebral glucose utilization (LCGU) in the brains of cirrhotic patients with mild-to-moderate HE. In one study, significant decreases in LCGU were observed in the anterior cingulate gyrus, a brain region known to be implicated in the mediation of attention as well as in target analysis and response formulation (30). These changes were accompanied by small but significant increases in LCGU in some other cortical and thalamic structures. This pattern of alterations of LCGU parallels the alterations in cerebral blood flow described in cirrhotic patients (31,32).

In a landmark study using PET and \(^13\)NH\(_3\), Lockwood et al. (33) were able to demonstrate an increase in the cerebral metabolic rate for ammonia (CMR\(_{\lambda}\)) (i.e. a measure of the rate at which ammonia is uptaken and metabolized by brain). Furthermore, this increased rate of ammonia utilization by brain was accompanied by an increase in the permeability/surface area product (PS), a measure of blood-brain barrier permeability to ammonia (Fig. 3).

This apparently increased ease with which ammonia moves from blood to brain in cirrhotic patients offers a plausible explanation for the imperfect correlation between neurological status and blood ammonia concentrations in these patients.

![Fig. 3. \(^13\)NH\(_3\)-positron emission tomographic images of a control subject compared to a cirrhotic patient with mild HE. Note increased CMR\(_{\lambda}\) and PS throughout the brain of the patient. CMR\(_{\lambda}\): Cerebral metabolic rate for ammonia. PS: Permeability surface area product. Adapted from ref. 33.](image-url)
Neurotoxic substances generated in chronic liver failure

Chronic liver failure and significant portal-systemic shunting result in the accumulation of neurotoxic substances in brain. Two such substances are ammonia and manganese.

Ammonia

Ammonia derived from colonic bacteria as well as from the deamination of glutamine in the small bowel is absorbed by passive diffusion and normally undergoes a high first-pass extraction by the liver (34). In chronic liver failure, hepatic urea synthesis declines and this, in addition to portal-systemic shunting, results in increased blood ammonia concentrations. Furthermore, cirrhotic patients are hypersensitive to ammoniagenic conditions such as an oral protein load or gastrointestinal hemorrhage. An illustration of this hypersensitivity is provided by a report of studies in the 1950's in which attempts were made to treat ascites in cirrhotic patients with ion-exchange resins that absorbed sodium but released ammonium ions (35). This treatment led to a significant reduction in ascitic volume but precipitated severe encephalopathy in many of the patients treated.

If present in high concentrations, ammonia has the potential to adversely affect central nervous system (CNS) function by several mechanisms. Such mechanisms include a direct effect of the ammonium ion \([\text{NH}_4^+]\) on inhibitory and excitatory neurotransmission (36) as well as inhibition of the tricarboxylic acid cycle enzyme ketoglutarate dehydrogenase (37) with potential impairment of brain energy metabolism. However, brain energy metabolism does not appear to be impaired in chronic liver failure until very late stages associated with isoelectric electroencephalography (EEG) traces (38). On the other hand, increases of cerebrospinal fluid lactate have been described both in cirrhotic patients with HE (39) and in experimental animals with chronic liver failure and ammonia-prefracipitated encephalopathy (40), findings which are consistent with an inhibitory effect of ammonia on cerebral glucose oxidation.

Other effects of ammonia on cerebral function include a stimulatory effect on L-arginine uptake by brain preparations resulting in increased production of nitric oxide (41) and inhibition of the capacity of astrocytes to accumulate glutamate (42,43), a major excitatory neurotransmitter.

Manganese

As previously mentioned in this review, chronic liver failure results in increased blood and brain concentrations of manganese (18.22-24) and manganese deposition is the most plausible explanation for the pallidal signal hyperintensities on MRI in cirrhotic patients. Manganese is neurotoxic, affecting both neuronal and astrocytic integrity. In the case of astrocytes, exposure to manganese results in altered expression of several key astrocytic proteins (44,45) and Alzheimer Type II changes (16).

Other toxins in addition to ammonia and manganese are known to increase in the systemic circulation in chronic liver failure. Such toxins include mercaptans, phenols and short chain fatty acids (46). While there is no convincing evidence that these toxins alone cause cerebral dysfunction in chronic liver failure, they could combine with ammonia or manganese to act synergistically (47).

Increased expression of genes coding for neurotransmitter-related proteins in brain in chronic liver failure

The lack of alterations in cerebral energy metabolism has resulted in a focus of attention on changes in brain neurotransmitter systems as the likely mediators of the neuropsychiatric manifestations of HE in chronic liver failure. Recent studies using molecular biological approaches continue to confirm that, when liver fails, brain responds with significant alterations in gene expression. In many cases these alterations involve genes which code for neurotransmitter-related proteins, many of which are essential for CNS function.

Monoamine oxidase (MAO-A isoenzyme)

Many of the symptoms of early HE in chronic liver failure such as altered personality, depression and inverted sleep patterns are symptoms which have classically been associated with alterations in biogenic amine function. RNA extracts of brain tissue obtained at autopsy from cirrhotic patients who died in hepatic coma have been found to show increased expression of the neuronal isoform of the monoamine-metabolizing enzyme MAO-A (48). This increase in MAO-A gene expression was found to be associated with increased activities of the enzyme and increased densities of catalytic sites on the enzyme protein (48). Moreover, studies of the same brain extracts revealed increased concentrations of homovanillic and 5-hydroxyindoleacetic acids (49) the final metabolites of dopamine and serotonin respectively. Increased concentrations of 5-hydroxyindoleacetic acid were also reported in cerebrospinal fluid from patients (50) and experimental animals (51) with chronic liver failure. On the basis of these findings, it has been suggested that altered monoaminergic function may be responsible for the early
neuropsychiatric symptoms of HE in chronic liver disease (51,52).

**The “peripheral-type” benzodiazepine receptor (PTBR)**

PTBR is a hetero-oligomeric protein complex located (like MAO-A) on the outer mitochondrial membrane of the astrocyte. Increased PTBR gene expression has been reported in brain extracts from portacaval-shunted rats (53). This increased gene expression resulted in increased receptor sites in the brains and peripheral tissues of these animals as revealed by quantitative receptor autoradiography and the highly selective PTBR ligand 3H-PK11195 (54,55). Increased 3H-PK11195 binding sites were also reported in autopsied brain tissue from cirrhotic patients who died in hepatic coma (56).

There is evidence to suggest that the increased expression of PTBRs in brain in chronic liver failure is the consequence of exposure to ammonia and/or manganese. Evidence in favor of this includes reports that: (i) increased densities of 3H-PK11195 binding sites are also observed in brain and peripheral tissues of mice with chronic hyperammonemia due to a congenital defect in the urea cycle enzyme ornithine carbamylase (57); (ii) exposure of rat cerebral cortical astrocytes in culture to ammonia results in increased densities of 3H-PK11195 binding sites (58); (iii) exposure to manganese also results in increased densities of 3H-PK11195 binding sites (44).

The precise mechanism whereby increased expression or activation of PTBRs results in altered brain excitability (characteristic of HE) has not been established. However, the mitochondrial localization of this receptor complex has led to the speculation that it plays a role in the maintenance of astrocytic energy metabolism and in the uptake of cholesterol by the mitochondria of these cells. This latter action results in the synthesis of a newly-characterized group of compounds known collectively as neurosteroids, some of which have potent neuroinhibitory properties (13). Further studies of neurosteroids in chronic liver failure and their possible role in the pathogenesis of HE are clearly warranted.

**Neuronal nitric oxide synthase (nNOS)**

Portacaval anastomosis in the rat results in increased gene expression of the constitutive (neuronal) isoform of nitric oxide synthase (nNOS) in brain (59). Increased nNOS mRNA is accompanied by increased nNOS protein (59) and by increased nNOS enzyme activities (41). There is recent evidence to suggest that, in addition to an induction in nNOS gene expression, increased nNOS activities may also result from a stimulatory effect of ammonia on L-arginine uptake by neuronal preparations (shown both in vitro and in vivo) (60). Increased production of nitric oxide as a consequence of increased nNOS activities could contribute to the alterations of nitric oxide synthase in chronic liver disease (61).

**Other neurotransmitter systems in HF**

The appearance of extrapyramidal symptoms (particularly rigidity) in cirrhotic patients with end-stage liver disease has prompted, by analogy with the well-established dopamine deficit in Parkinson’s Disease, evaluations of the dopamine system in relation to HE. Studies in autopsied brain tissue from cirrhotic patients (49) and from rats with portacaval shunts (51) reveal several-fold increases in concentration of the dopamine metabolite homovanillic acid, a finding which could result from increased activities of monoamine oxidase reported in the same material (48) (see above). In another study, densities of the postsynaptic dopamine D2 receptor were significantly reduced in pallidum/putamen from cirrhotic patients (62), a finding that could have resulted from manganese deposition in the brains of these patients (22).

Cirrhotic patients are hypersensitive to morphine (63) and portacaval shunting in the rat results in increased pain sensitivity (64), a phenomenon known to involve the endogenous opioid system. Increased plasma levels of the endogenous opioid met-enkephalin have been recorded in patients with primary biliary cirrhosis (65) and brain β-endorphin levels are increased in experimental chronic liver failure (66). β endorphin is an endogenous opioid peptide that is involved in the positive reinforcing effects of drugs of abuse, including ethanol (67). It is of interest, therefore, that portacaval-shunted rats drink significantly more ethanol in a free-choice drinking paradigm (68,69). Autoradiographic studies in the brains of these animals reveal region-selective alterations of μ and δ opioid receptor sites (70). Moreover, the increase in ethanol preference manifested by the rats after portacaval shunting is significantly attenuated following administration of the opioid receptor antagonist naloxone (69). Extrapolation of these findings to humans suggests the intriguing possibility that significant liver disease and portal systemic shunting could result in activation of the brain opioid system with the potential to lead to increased drinking.

**Prevention and treatment of HE**

Strategies aimed at the prevention and treatment of HE in chronic liver failure are of two major types,
namely, ammonia-lowering strategies and approaches aimed directly at the CNS (34,71).

**Ammonia-lowering strategies**

Since HE is frequently precipitated by ammoniagenic situations such as an oral protein load or a gastrointestinal hemorrhage, various treatment modalities are aimed at the gut. Such strategies include reduction of the absorption of nitrogenous substances arising from bacterial action in the colon. Colonic cleansing reduces the luminal ammonia content and lowers blood ammonia content in cirrhotic patients (72).

Non-absorbable disaccharides such as lactulose are routinely used to decrease ammonia production in the gut. The action of the most popular substance in this class, lactulose, involves increased fecal nitrogen excretion by facilitation of the incorporation of ammonia into bacteria as well as a cathartic effect (34). Lactulose administered orally reaches the cecum where it is metabolized by enteric bacteria, causing a fall in pH (73). The dose is adjusted to produce two or three soft bowel movements daily (34).

Antibiotics such as neomycin are also useful for lowering blood ammonia, mainly by an effect on ammonia production by intestinal bacteria. However, neomycin therapy is associated with significant toxic side effects (34).

Restriction of dietary protein remains a cornerstone of therapy for HE in cirrhotic patients (34). However, long-term nitrogen restriction is potentially harmful and a positive nitrogen balance is necessary to promote liver regeneration as well as to increase the capacity of skeletal muscle to remove ammonia in the form of glutamine (74). Protein intake of 1-2 g/kg per day may be required in order to maintain an adequate nitrogen balance (75).

An alternative strategy for the lowering of blood ammonia is the stimulation of ammonia fixation (71). Under normal physiological conditions, ammonia is removed by the formation of urea in periportal hepatocytes and by glutamine synthesis in perivenous hepatocytes, skeletal muscle and brain. In cirrhosis, both urea cycle enzymes and glutamine synthetase in liver are decreased in activity. Strategies to stimulate residual urea cycle activities and/or glutamine synthesis have been tried over the last 20 yr. One of most successful agents to be used so far is L-ornithine-L-aspartate (OA). Randomized controlled clinical trials with OA demonstrate significant ammonia lowering and concomitant improvement in psychometric test scores in cirrhotic patients with HE (76). Studies in experimental animals suggest that the metabolic basis for the beneficial effect of OA on blood ammonia in chronic liver failure resides in its ability to stimulate residual hepatic urea cycle function and also to promote glutamine synthesis, particularly in skeletal muscle (77).

Benzoate is also effective in reducing blood ammonia both in patients with inherited urea cycle disorders and in cirrhotic patients (71). In a randomized controlled clinical trial with sodium benzoate versus lactulose, improvement in neuropsychiatric performance was found to be comparable using both treatments (78).

**Use of CNS-acting drugs**

In contrast to the multiple strategies used successfully to lower blood ammonia and improve neurological status in patients with chronic liver failure (above), drugs which act directly on neuronal excitability have not been widely applied in this patient group. The major reason for this is that the precise neurotransmitter changes responsible for HE in chronic liver failure are still being elucidated. Some attempts to treat HE in cirrhotic patients with benzodiazepine receptor antagonists and dopamine agonists have been attempted, but with limited success.

Several controlled clinical trials have been performed to assess the efficacy of the benzodiazepine receptor antagonist flumazenil in cirrhotic patients with various degrees of severity of HE (71). Spectacular improvements in neuropsychiatric status were recorded in a subset of patients receiving flumazenil (79,80). However, enthusiasm for this approach has been tempered by the possible confounding effects of prior exposure to benzodiazepines and the seeming lack of correlation between clinical response and blood levels of substances with benzodiazepine receptor agonist properties in these patients (81).

Drugs known to increase dopaminergic neurotransmission such as L-DOPA and the dopamine receptor agonist bromocriptine have been used in clinical trials in cirrhotic patients with HE. Results were not encouraging in terms of improvement of overall neuropsychiatric status (82,83). However, it is possible that these agents could improve motor performance in these patients (34).

It is anticipated that new therapeutic avenues will emerge as the precise abnormalities in the monoaminergic, glutamatergic and opioidergic systems become more clearly defined in relation to the various cognitive, psychiatric and motor symptoms that characterize HE in chronic liver failure.

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