

Editorial

## Treatment for hepatic encephalopathy: tips from TIPS?

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The advent of evidence based medicine has resulted in scrutiny of many of the treatment options already entrenched in clinical practice. The results have at times comforted, at other disconcerted and, in the case of the recent reappraisals of the treatment of hepatic encephalopathy in patients with cirrhosis, only served to confuse [1–7].

Treatment of this condition is based, somewhat empirically, on the simplest of the proposed pathogenic mechanisms, namely the generation of gut-derived neurotoxins [8], which are ineffectually detoxified, or bypass the liver, and impinge on the brain. Supportive care and the treatment of any precipitating factors may result in considerable improvement in the status of patients with episodic, overt hepatic encephalopathy but the mainstays of treatment are enemata, non-absorbable disaccharides and non-absorbable antibiotics. These agents reduce the circulating toxin load by a variety of means but their effects are broad based rather than specific.

Assessing the efficacy of treatment for this condition has always been difficult because of the wide spectrum of neuropsychiatric abnormalities encompassed by the diagnosis, the lack of agreement on the methods best used to quantify treatment effects/endpoints and the difficulties encountered in selecting appropriate control regimens. The non-absorbable disaccharides, for example, have a pronounced cathartic effect so use of an inert comparator would unblind the observations whilst adding a laxative to the control regimen might confound the results. Thus, the initial assessments of the efficacy of lactulose as a treatment for hepatic encephalopathy were, overall, not well controlled although it is still unclear how a blinded assessment against

an inert comparator could be achieved. Nevertheless lactulose, and later lactitol, were introduced as standard treatment for this condition. It follows that the majority of subsequent treatment trials used the non-absorbable disaccharides as the control option as it was considered unethical to use a placebo preparation. Thus, the efficacy of any new therapeutic agent or manoeuvre was judged against a treatment of apparently unproven worth.

Given the apparent shortcomings of these treatment trials a review of treatment efficacy in hepatic encephalopathy is clearly warranted and members of the Cochrane Collaboration are to be commended for undertaking this task [1–7]. However, their systematic reviews can be criticised for a number of reasons but mainly because of the choice of variables used to assess treatment efficacy.

The primary outcome measures selected were ‘all cause mortality’ and the rather cumbersome ‘number of patients without improvement of hepatic encephalopathy’. Short-term mortality rates are low in these trials mainly because unstable patients, or those unlikely to survive the trial period, tend to be excluded; assessment of this variable is, therefore, of limited value. On the other hand, an assessment of ‘improvement’, or a lack thereof, should have provided valuable information on treatment efficacy. However ‘improvement’ was defined for purposes of these reviews as ‘partial or complete resolution of clinical or subclinical symptoms of hepatic encephalopathy’. This is not further explained nor is any clue to the totally meaningless of ‘subclinical symptoms’ provided. The reviewers presumably based their assessment of improvement, at least in the patients with overt hepatic encephalopathy, on reported changes in their clinical grading, although this is prone to significant inter- and intra-observer error and does not provide an objective measure of status. Alternatively they may have based their

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assessment of improvement on the authors' interpretation of observed and measured variables, although this would certainly have compromised the independence of the review by introducing bias.

The Cochrane reviewers concluded that there was insufficient evidence to determine whether non-absorbable disaccharides are of benefit in patients with hepatic encephalopathy [4,7]. They further concluded that antibiotics were therapeutically superior to non-absorbable disaccharides even though they did not assess or include any of the placebo-controlled antibiotic trials [4,7]. However, these conclusions must be viewed with caution as they are not based on a sufficiently rigorous assessment of the available data and should certainly not be interpreted as indicating that lactulose is an ineffective treatment for hepatic encephalopathy [9].

The question of the efficacy of treatment for hepatic encephalopathy and the difficulties inherent in its assessment are further highlighted in a study undertaken by Riggio and coworkers and reported in this issue of the Journal [10]. This study focuses on the efficacy of pharmacological prophylaxis for the prevention of hepatic encephalopathy following placement of a transjugular intrahepatic portosystemic shunt (TIPS). Approximately 20 to 50% of shunted patients develop some degree of neuropsychiatric impairment in the first 6 months after TIPS placement, most frequently in the first month after the procedure. The encephalopathy is generally easily treated but 1–5% of the shunted patients develop chronic intractable neuropsychiatric symptoms, which only resolve when the shunt is reduced or revised [11–13].

Riggio and colleagues [10] randomized 75 patients, immediately after successful TIPS placement, to either 'no treatment' or to treatment, for one month, with lactitol (60g/day) or rifaximin (1200 mg/day). During the study period 33% of the patients developed at least one episode of clinically apparent (Grade II) hepatic encephalopathy, which was the main study end-point. There was no significant difference in the incidence of encephalopathy in the three randomized groups. Not surprisingly the authors concluded that lactitol and rifaximin are ineffective prophylactic agents in this setting. Overall this study was well designed and executed but there are a number of issues that may have affected the results and hence the conclusions drawn.

The authors concede that their study was underpowered. In calculating their sample size they assumed that 40% of the untreated patients would develop hepatic encephalopathy post-TIPS and that either of the two treatments would reduce the incidence to 10%. Despite this miscalculation the authors felt that their study was so convincingly negative that it is unlikely that significant treatment differences would emerge even with a much larger sample size. This is a moot point.

There are, however, other issues with the study design, which are not as easily dismissed. The main issue is the real nature of the proffered 'no treatment' option. Avoidance of constipation is one of the mainstays of encephalopathy

prevention and in this study patients in the 'no treatment' arm, and those receiving rifaximin, were given sorbitol enemas, throughout the trial, on days when they did not open their bowels naturally. However, sorbitol is a non-absorbable sugar alcohol, which is metabolised by colonic bacteria in a similar manner to the non-absorbable disaccharides and, like them, causes colonic acidification [14–16]. It has also been shown to improve psychomotor performance when given to cirrhotic patients [16]. Thus, sorbitol is far from an inert aperient and its use in earlier studies comparing the efficacy of lactulose and neomycin [17,18] might have resulted in an underestimate of the beneficial effects of the non-absorbable disaccharide.

Riggio and colleagues [10] did not provide any quantitative data on sorbitol usage by the patients in their study. Infrequent or occasional use by some of the patients in the 'no treatment' and rifaximin groups would probably have had little overall effect. However, more frequent or regular usage by a reasonable number of these patients might have influenced the outcome. The need to avoid constipation in this patient population is one of the major issues in trial design particularly if one of the study treatments has an intrinsic laxative effect.

Another factor that may have influenced the results is the possibility that the patients in the three randomized groups were not as comparable as they seemed. The TIPS procedure was undertaken electively in 83% of the patients who were hospitalized for *at least* 5 days beforehand. An unspecified number had been on long-term treatment with non-absorbable disaccharides or antibiotics but this was stopped on admission. These patients would be more likely to develop hepatic encephalopathy post-procedure than their previously untreated counterparts. This is a potential source of bias that is not entirely countered by the fact that there were no apparent differences in patient characteristics in the three randomized groups. The patients' mental state may not have caused alarm when they were assessed the day before the TIPS procedure because most treatments for hepatic encephalopathy have a washout effect but their susceptibility to develop encephalopathy will most certainly have been heightened. If these previously treated patients were unevenly randomized following the procedure then this might have biased the results.

One important point highlighted by this study is the difference between prophylaxis and treatment. Lactitol and rifaximin were not effective as prophylactic agents and yet the patients who developed overt hepatic encephalopathy post-procedure responded promptly when treated fairly simply with little more than transient protein restriction and lactitol enemas. Thus, the fact that a drug is apparently ineffective in one setting does not imply that it is entirely ineffective without therapeutic efficacy. Treatment was only provided for a month following the TIPS procedure and so no comments can be made about the therapeutic efficacy of the trial medications beyond this time.

The TIPS ‘model’ of hepatic encephalopathy is difficult to characterize and thus the applicability of information derived from this model to the other forms of hepatic encephalopathy is unclear. The patients who undergo this procedure will invariably have chronic liver disease and varying degrees of hepatocellular dysfunction/portal systemic shunting. The procedure, if successful, significantly alters portal haemodynamics and in consequence the circulating toxin load. However, only a percentage of patients develop hepatic encephalopathy post-procedure. Riggio and colleagues [10] provide valuable information on the factors likely to predispose to the development of this condition and emphasize that the best way to prevent its occurrence is by rigorous application of well-defined selection criteria. A number of risk factors have been identified but probably the most important relate to the patients’ past and current neuropsychiatric status. Patients with a history of either persistent, multiple or even single previous episodes of encephalopathy are at greater risk [10, 12]. In addition, impaired performance of the single psychometric test performed in this study carried a significant risk hazard [10]. It is highly likely that a more detailed assessment of the patients’ neuropsychometric/neurophysiological status would provide a more comprehensive picture of the risk hazards for individual patients. The incidence of post-TIPS encephalopathy decreases with time most likely due to shunt stenosis [12]. However, the new generation of covered stents are less likely to stenose and are more likely to be associated with the development of persistent post-shunt encephalopathy [13]. Even more rigorous selection procedures will, therefore, be needed. A number of assessment tools are available the majority of which are easily applied and readily accessible [19–21].

This study by Riggio and colleagues [10] highlights further the issue of the efficacy of treatment for hepatic encephalopathy. Calls for further studies should not be heeded until the body of data already available has been fully appraised, and should not be implemented, even where indicated, until methods for assessing neuropsychiatric status have been standardised, appropriate study end-points agreed and study designs established which take into account the need to maintain blinding without compromising the integrity of the therapeutic regimens under test.

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