Management of Overt Hepatic Encephalopathy

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Hepatic encephalopathy (HE) is an important complication of cirrhosis with significant morbidity and mortality. Management of HE primarily involves avoidance of precipitating factors and administration of various ammonia-lowering therapies such as non-absorbable disaccharides, antimicrobial agents like rifaximin and L-ornithine L-aspartate. The non-absorbable disaccharides which include lactulose and lactitol are considered the first-line therapy for the treatment of HE and in primary and secondary prophylaxis of HE. Lactitol is comparable to lactulose in the treatment of HE with fewer side effects. Rifaximin is effective in treatment of HE and recent systemic reviews found it comparable to disaccharides and is effective in secondary prophylaxis of HE. Many agents like L-ornithine L-aspartate, probiotics, zinc, sodium benzoate have been tried either alone or in combination with lactulose for the treatment of HE. Combination therapy of disaccharides either with rifaximin, L-ornithine L-aspartate, probiotics for the treatment of HE needs further validation in large studies. (J Clin Exp Hepatol 2015;5:S82–S87)

Treatment

Hepatic encephalopathy (HE) is a complex neuropsychiatric syndrome, which may complicate acute, chronic liver failure or patients with portal-systemic shunting. It is characterized by changes in mental state including a wide range of neuropsychiatric symptoms ranging from minor signs of altered brain function to deep coma.[1,2] It is one of the commonest indications for admission in intensive care unit in patients with advanced cirrhosis. There were over 40 000 patients hospitalized in the United States alone for a primary diagnosis of HE, resulting in total charges of approximately $932 million. Data in other countries are lacking, hence it causes a huge burden financially to the patient and society.[3]

The West Haven Criteria are most often used to grade HE, with scores ranging from I–IV (IV being coma). However, it is a challenge to diagnose patients with minimal hepatic encephalopathy (MHE) or grade 1 HE; so it might be practical to combine these entities and name them covert HE for clinical use and overt HE to patients with grade II to IV.[1,4,5] One of the major tenets of the pathophysiology of HE is hyperammonemia that results from an increased nitrogenous load from the gastrointestinal tract and reduced urea synthesis both due to portal-systemic shunting and decreased urea hepatic synthesis. Brain and skeletal muscle neither remove nor produce ammonium in normal conditions, but they are able to seize ammonium during hyperammonemia, releasing glutamine. Ammonia is produced both by bacterial degradation of amines, aminoacids, purines, and urea as well as enterocytic glutaminase activity that converts glutamine to glutamate and ammonia.[6,7] Astrocytes play an important role in the pathogenesis of HE with consequences for neuronal function. Astrocytes have the ability to eliminate ammonia by the synthesis of glutamine through amidation of glutamate by the enzyme glutamine synthetase Hyperammonemia leads to the accumulation of glutamine within astrocytes, which exerts an osmotic stress that causes astrocytes to take in water and swell.[8,9]

This article reviewed the clinical impact, pathogenesis, and management of overt HE in patients with cirrhosis. Articles published between January 1960 and November 2013 were acquired through a MEDLINE search of different combinations of the terms hepatic encephalopathy, pathophysiology, treatment, prophylaxis, prognosis, and recurrence. Randomized trials, open-labeled trials and meta-analysis on HE which were published in English literature were included for this review.

THERAPY FOR HEPATIC ENCEPHALOPATHY AND ROLE OF NON-ABSORBABLE DISACCHARIDES

The first step in treatment of HE is identifying and treating precipitating causes which includes management of hypovolemia, gastrointestinal bleeding, infection, excessive diuretic use, diarrhea, vomiting, hyponatremia, hypokalemia or hyperkalemia, constipation,

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Abbreviations: HE: hepatic encephalopathy; MHE: minimal hepatic encephalopathy; TIPS: transjugular intrahepatic portosystemic shunt; HR: hazard ratio
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benzodiazepine use and noncompliance with lactulose or rifaximin therapy.[2]

Non-absorbable Disaccharides and Mechanism of Action

Current therapies for HE are based on ammonia-lowering with the hypothesis that the colon is the primary organ that generates ammonia. Non-absorbable disaccharides have been the first-line drug treatment for lowering the production and absorption of ammonia.[2,10] Disaccharides (lactulose and lactitol) get metabolized by the bacteria in the colon to acetic and lactic acid. This acidification of the colon not only creates a hostile environment for the survival of intestinal bacteria with urease activity involved in the production of ammonia in the gut, but also facilitates the conversion of NH3 to non-absorbable NH4+. Both effects result in reduced levels of ammonia in the colon and portal blood. Non-absorbable disaccharides also cause a 4-fold increase in faecal nitrogen excretion due to their cathartic effect.[11,12]

Lactulose is the most commonly utilized non-absorbable disaccharide for HE. Lactulose, a synthetic disaccharide, is comprised of the monosaccharides lactose and galactose, and is available as syrup and powder. Similarly lactitol (p-galactosido–sorbitol) is a disaccharide analog of lactulose which is neither absorbed nor broken down in the small intestine. Doses are generally titrated to achieve two to four semi-soft stools daily.

Clinical Efficacy of Non-absorbable Disaccharides

The non-absorbable disaccharides have been a mainstay of therapy for HE for decades, and have been extensively studied in several small clinical trials. Oral lactulose was used in majority of these studies though some had used lactitol and lactulose enemas also.[13,14] In most of the studies the daily mean doses of lactulose ranged from 30 g to 80 g (median 50 g) to obtain two to three semi-soft stools per day. The median duration of treatment was 15 days (range 5–360 days). Lactitol has also been used in treatment of HE and meta-analysis showed no statistical differences in percentage of improved patients after lactitol or lactulose while slightly higher frequency of flatulence in patients treated with lactulose compared with lactitol[15–19] (Table 1).

A recent meta-analysis evaluated 22 clinical trials in order to better assess the utilization of non-absorbable disaccharides in the management of HE when compared with placebo, no intervention or antimicrobials. Compared with placebo or no intervention, lactulose and lactitol seemed to reduce the risk of no improvement of hepatic encephalopathy (relative risk 0.62, 95% confidence interval 0.46–0.84). However high quality trials found no significant effect of lactulose or lactitol on the risk of no improvement (0.92, 0.42–2.04), whereas low quality trials found a significant beneficial effect of lactulose or lactitol (0.57, 0.40–0.83).[20] Most of the studies were carried out in adults however lactulose has shown to be effective in the treatment of HE in children also.[21] At present time, however, there is a lack of sufficient evidence to thoroughly refute the use of non-absorbable disaccharides for the treatment of HE. We analyzed the factors associated with non-response to lactulose therapy and found that high baseline MELD, high total leukocyte count, low serum sodium, low MAP, and presence of hepatocellular carcinoma were predictors of nonresponse to lactulose.[22]

ANTIMICROBIAL AGENTS FOR HEPATIC ENCEPHALOPATHY

Antimicrobial agents have long been utilized for the treatment of patients with overt HE. Neomycin and other antimicrobials are utilized as a treatment modality in HE due to their ability to inhibit ammonia production by intestinal bacteria.[23] Other antimicrobials, including metronidazole and vancomycin, have been studied to a more limited extent than neomycin.[24,25]

Rifaximin for Hepatic Encephalopathy

Rifaximin is a poorly absorbed synthetic antimicrobial with a broad spectrum of antibacterial activity. Both

Table 1 Comparison of Non-absorbable Disaccharides and Placebo or No Treatment for Hepatic Encephalopathy.

Trial	Study design	Patients	No	Treatment	Assessment	Efficacy
Simmons et al[13]	Parallel	AHE + CHE	26	Lactulose/glucose	Clinical grading, ammonia, stool production	Lactulose = glucose
Uribe et al[14]	Parallel	AHE	15	Lactulose enema	Mortality, clinical grading	Lactulose > placebo
Lanthier et al[15]	Crossover	CHE	5	6 months	Clinical examination, psychometric tests, ammonia levels, EEG, cerebral blood flow	Lactulose = lactitol
Heredia et al[16]	Parallel	AHE	40	5 days	Mortality, clinical grading, PSE grade, adverse events	Lactulose = lactitol
Riggio et al[17]	Parallel	CHE + MHE	31	6 months	PSE index, new episodes of HE, adverse events	Lactulose = lactitol

AHE: acute hepatic encephalopathy; CHE: Chronic hepatic encephalopathy; MHE: Minimal hepatic encephalopathy; EEG: Electroencephalography.