

New strategies for treating hepatic encephalopathy

Cristina Gómez-Gutiérrez, María C. Manzano-Robleda, Misael Uribe, Nahum Méndez-Sánchez

Liver Research Unit, Medica Sur Clinic & Foundation, Mexico City, Mexico.

Article commented

Rockey DC, Vierling JM, Mantry P, Ghabril M, Brown Jr., RS, Alexeeva O, Zupanets IA, et al. For the HALT-HE Study Group. Randomized, double-blind, controlled study of glycerol phenylbutyrate in hepatic encephalopathy. *Hepatology* 2014; 59: 1073-83.

Comment

Hepatic encephalopathy (HE) is a serious neuropsychiatric complication of both acute and chronic liver disease. Historically, the role of ammonia accumulation has dominated explanations of the pathogenesis of HE. However, evidence has emerged for a role of other concurrent factors such as inflammation, hyponatremia, neurosteroids, oxidative and nitrosative stress, manganese with cerebral edema. The precise molecular mechanisms that cause these changes in the brain, are not completely understood.¹ The general management of HE focuses on providing supportive care, identifying and treating any precipitating causes, reducing nitrogenous load in the gut, and assessing the need for long-term therapy and liver transplant evaluation.^{2,3} A long-term therapeutic intervention to prevent recurrent HE is needed to decrease health care burden, improve quality of life, and improve outcomes for chronically ill patients. One of the most used pharmacology intervention in these patients are nonabsorbable disaccharides (lactulose or lactitol)

consider as the first-line therapy by acting in the intraluminal gut bacteria promoting the formation of the less permeable ammonium ion (NH₄⁺) from ammoniac (NH₃) and as an osmotic laxative that decrease the time available for absorption. When compare the use of lactulose versus placebo, the treated patients show less overt HE (11 vs. 28%, p 0.02).⁴ Rifaximin is another important long term pharmacological measurement for HE, these oral antimicrobial agent has a gut-selective activity with nonsystemic effect being a safe drug with no increase in the rate of infections or development of bacterial antibiotic resistance.⁵ When compared efficacy of rifaximin plus lactulose vs. lactulose alone for treatment of overt HE in a prospective double-blind randomized controlled trial, demonstrated that combination of lactulose plus rifaximin is more effective than lactulose alone in achieving complete reversal of HE (76 vs. 50% p 0.004) and also decrease mortality (23.8 vs. 49.1%, p < 0.05).⁶ On the other hand, a very important area in the management of HE consist on nutritional support, being protein and energy one of the most important, in 2013 a International Society for Hepatic Encephalopathy and Nitrogen Metabolism Consensus proposed that the optimal daily energy intake should be 35-40 kcal/kg ideal body weight (recommendation 1A) and the optimal daily protein intake should be 1.2-1.5 g/kg ideal body weight (recommendation 1A), small meals should be evenly distributed throughout the day and a late-night and a snack of complex carbohydrate will minimize protein utilization (recommendation 1A).⁷

Among the variety of pharmacology options available for treat HE, Glycerol Phenylbutyrate (GPB) approved in 2013 for the Food and Drug Administration in the US for the treatment of urea cycle disorders, provides an alternate pathway for ammonia removal by urine.^{8,9} The paper of Rockey, *et al.* published on march 2014 in *Hepatology*¹⁰ proposes another application of these drug beyond the urea cycle disorders, like a potential therapeutic option for HE in patients with preexistent HE. GPB is com-

Correspondence and reprint request: Prof. Nahum Méndez-Sánchez, MD, MSc, PhD, FACC, AGAF.
Liver Research Unit, Medica Sur Clinic & Foundation.
Puente de Piedra 150, Col. Toriello Guerra, Tlalpan 14050, Mexico City, Mexico.
Phone: (+52) 55424-7200. Ext. 4215;
Fax: (+52)55 666-4031.
E mail: nmendez@medicasur.org.mx

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posed by three molecules of phenylbutyric acid (PBA) joined to glycerol by ester, it is metabolized to the same active substance, phenylacetic acid (PAA), when these metabolite is conjugated with glutamine (a temporary storage form of ammonia) form phenylacetylglutamine and as such is then eliminated by the kidneys as phenylacetyl glutamine (PAGN).¹⁰ In 2010, McGuire, *et al.* studied the pharmacology and safety profile of GPB in healthy and cirrhotic patients and found that is well tolerated in adults with cirrhosis suggesting its use as a potential alternative for treating HE.¹¹ Rockey, *et al.*, design a 4-week open-label, multicenter, randomized, double-blind, placebo-controlled phase II study where 6 mL of GPB was given orally twice-daily to adult patients with cirrhosis who had experienced at least two episodes of HE or West Haven grade 2 or greater in the previous 6 months one of which was within 3 months of randomization, they include patients taking rifaximin with the specification of at least one of their two qualifying HE events after taking rifaximin for at least 1 month. They performed an intention to treat analysis, express as a proportion of patients experimenting an HE event. The secondary endpoints were to analyze the time to first HE events and total HE events. The trial present a total of 178 patients, even though the predetermined sample size was calculated for 186 patients for a 80% power to detect an expected 50% treatment effect. The patients included were of 35 in the United States, 7 in the Ukraine, and 9 in Russia from June 1, 2010 to October 31, 2011. The most important results of these multicenter trial are that patients in the GPB group experienced fewer HE events than placebo group (21 *vs.* 36%, respectively; $p < 0.02$), the total number of HE events was also lower in the treatment arm (35 *vs.* 57 in the placebo arm; $p < 0.04$) and fewer dose interruptions (3 patients with 4 total interruptions *vs.* 15 patients with 27 total interruptions; $p < 0.01$). These statistically significant effect was only evaluated in overt HE. When the analysis of the on-rifaximin and off-rifaximin baseline state was made, the 119 off-rifaximin taking GPB had a significant reduction both the proportion of patients with at least one HE event and in total events. On the other hand the proportion of patients with at least one HE event was similar in the two treatment arms in the 59 patients on-rifaximin at baseline, there was non-significant difference in favor of fewer total HE events on the GPB arm. The effect of baseline use of lactulose was also analyzed, and the authors observed that the time to the first HE event was lower in the treat-

ment arm (22 *vs.* 45% $p < 0.01$). One unexpected result was that patients on rifaximin group had higher ammonia, these might reflect that patients on-rifaximin at baseline had more severe disease. Is important to clear that in these trial the frequency and types of adverse events in the two treatment arms were similar, being the gastrointestinal disorders (nausea and vomiting) the most commonly presented. These clinical trial published by Rockey definitely demonstrate that the use of GPB, a simple tasteless sodium-free liquid drug with no serious adverse event, reduce the likelihood of HE events in patients with preexisting HE and that ammonia still is a determinant in the development of HE. The favorable effect of the drug remains positive in patients taking lactulose as a baseline anti-ammonia measure but not in those taking rifaximin. The use of GPB appears safe, and well tolerated anti-ammonia measurement so clinicians can expect a better compliance a very important issue in preventing new HE events. But not everything is so pretty, one disadvantage is the cost of these new promising drug, when it is used for urea cycle disorders is priced is about \$250,000 to \$290,000/per year, of course in these context the price is difficult to calculate because here only adults were included and it is a different disease.¹⁰ These promising drug definitely reduce HE events in patients with preexisting HE but other clinical fields should be investigated, that is the case of minimal HE (MHE). Because the treatment of patients with MHE warranted improvement on their quality of life.¹² In this context would be an interesting field of research. Rockey, *et al.* demonstrated that GPB reduced the likelihood of HE events in patients with preexisting HE and the results suggest that elevated blood ammonia plays an important role in the pathogenesis of recurrent overt HE, and therefore it deserves further study as a potential therapeutic option in larger groups of cirrhotic patients.

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