Primary Prophylaxis to prevent the development of Hepatic Encephalopathy in Cirrhotic Patients with Acute Variceal Bleeding

Hepatic encephalopathy (HE) is a neurological disorder caused by the accumulation of toxic substances in the blood due to the inability of liver to perform it's detoxification functions [1], it's development deteriorates the cognitive function in cirrhotic patients and predisposes these patients to risks, such as increased frequency of falls, which will effect there quality of life negatively [2,3], also severe cases had led to coma and death [3]. Ammonium plays an important role in the pathophysiology of this disorder, and currently available treatments for HE are designed to reduce the production and intestinal absorption of ammonium or to promote it's metabolism and these treatments include nonabsorbable disaccharides such as lactulose, antibiotic that acts in intestinal lumen such as rifaximin, and drugs favoring extrahepatic metabolism of ammonium such as L-ornithine L-aspartate (LOLA) [(4-7)]. The development of HE is a well-known complication in patients with acute variceal bleeding (AVB) [(8-10)], the incidence ranges from 16.9 to 40% [9,10], it happens through the absorption of toxic products such as ammonium. To date, only two nonblinded studies have evaluated oral administration of lactulose versus placebo, demonstrating that lactulose is an effective therapy to prevent the development of HE after an AVB [9,10].

A recent randomized, double-blinded, controlled clinical trial published in10 July 2018, and was performed at "Hospital General de M´exico", aimed to compare whether the clinical effect of primary prophylaxis with lactulose or LOLA or rifaximin in cirrhotic patients with AVB is better than placebo for preventing the development of HE, by recruiting Cirrhotic patients with both genders, admitted to hospital for AVB, without Minimal Hepatic Encephalopathy (MHE), based on the development of Overt Hepatic Encephalopathy (OHE) in the first week (7 days) after an AVB, the time in days for the development of OHE after an AVB; also the late occurrence of OHE on the first 28 days after an AVB. A total of 103 patients who agreed to participate in the study and met the selection criteria were included in the study, 15 of them met some exclusion criteria. 88 patients (22 patients per group) were randomized to one of four possible groups (A, B, C or D), but one in group C finally withdrew his consent to participate in the study. The investigator was blinded to the drugs administered in each group and only knew the group by it's letter. Group A was treated with lactulose (Lactulax) orally, 30 mL every 8 hours, while patients had residual melena; then it was adjusted by increasing or reducing the dose to 10 ml every day according to the dose response to achieve two to three daily soft stools. Group B was treated with LOLA (Hepa-Merz) intravenous infusion (500 ml of saline solution containing 10 grams of LOLA for 24

hours). Group C was treated with rifaximin (Flonorm) administered at a standard dose of 400 mg orally every 8 hours. Group D was the control group that received all the corresponding placebos to achieve blinding of the study; patients in this group received an intravenous glucose solution of 5% for 24 hours, dextrose solution of 30 ml orally every 8 hours, adjusted equally as mentioned for lactulose dose, and 2 dextrose tablets orally every 8 hours in similar size, color, and shape to the rifaximin tablets. Groups A, B, and C also received treatment corresponding to the complementary placebos to ensure that both the investigator and the patient were blind towards the prophylaxis maneuver they were receiving. Treatment duration was 7 days in all groups. Patients were reassessed daily through West- Haven scale and systematic neurological exploration searching or OHE. Laboratory controls including ; urea, creatinine, sodium, chlorine, potassium, bilirubin, albumin, also hemoglobin, leukocytes count, platelets count, prothrombin time, and INR were taken on day 3 and on day 7, after 7 complete days of therapy and follow-up, stable patients without additional complications were discharged for outpatient follow-up. Only those patients who required treatment due to development of OHE or any other complications stayed in hospital for management. Thereafter, all patients were reassessed every week until 28-day follow-up searching for late complications.[11]

The results show that in the placebo group 12/22 patients (54.5%) developed OHE after the AVB episode; in the lactulose group this occurred in 6/22 patients (27.3%); in the group receiving LOLA this occurred in 5/22 patients (22.7%); and in the group receiving rifaximin this occurred in 5/21 patients (23.8%). Comparatively with placebo, the frequency regarding the development of OHE was as follows: lactulose (54.5% versus 27.3% P = 0.06); LOLA (54.5% versus 22.7%, *P* = 0.03); rifaximin (54.5% versus 23.8%, *P* = 0.04). When the three groups that received antiammonium therapies were compared, there was no significant differences between the three groups (P = 0.94). Regarding the time in days from admission to the development of OHE among those who developed it was as follows: lactulose, median 2.5 (range: 2-4); LOLA, median 3 (range: 1-3); rifaximin, median 3 (range: 1-4); placebo, median 2 (range 1-4); *P* = 0.88. Nobody developed OHE beyond day 4 on 28- day follow-up. Regarding the degree of OHE according to the West- Haven criteria, the degree of OHE was more severe in those who received placebo (median 3, range 2-4) compared to those who received any antiammonium prophylactic measure: LOLA (median 1, range 1-2) (P = 0.04); rifaximin (median 2, range 1 to 3) (P = 0.05); and lactulose (median 2, range: 1 to 3) (P = 0.02).[11]

In conclusion, the study showed that early primary prophylaxis with antiammonium drugs, particularly LOLA and rifaximin, seems to be a promising clinical strategy, effective and safe to avoid the development of OHE in cirrhotic patients with AVB. The most important risk factor associated with the development of OHE was the recurrence of the AVB.

References:

1. P. Ferenci, A. Lockwood, K. Mullen, R. Tarter, K.Weissenborn, andA. T. Blei, "Hepatic encephalopathy—definition, nomenclature, diagnosis, and quantification: final report of the Working Party at the 11thWorldCongresses of Gastroenterology,Vienna, 1998," Hepatology, vol. 35, no. 3, pp. 716–721, 2002.
2. E. Rom´an, J. C´ordoba, M. Torrens, C. Guarner, andG. Soriano, "Falls and cognitive dysfunction impair health-related quality of life in patients with cirrhosis," European Journal of Gastroenterology & Hepatology, vol. 25, no. 1, pp. 77–84, 2013.
3. J. Bustamante, A. Rimola, P.-J. Ventura et al., "Prognostic significance of hepatic encephalopathy in patients with cirrhosis," Journal of Hepatology, vol. 30, no. 5, pp. 890–895, 1999.
4. V. Khungar and F. Poordad, "Hepatic Encephalopathy," Clinics in Liver Disease, vol. 16, no. 2, pp. 301–320, 2012.
5. M. Luo, L. Li, C.-Z. Lu, and W.-K. Cao, "Clinical efficacy and safety of lactulose forminimal hepatic encephalopathy: Ametaanalysis," European Journal of Gastroenterology & Hepatology, vol. 23, no. 12, pp. 1250–1257, 2011.
6. J. P. Ong, G. Oehler, C. Kr¨uger-Jansen, J. Lambert-Baumann, and Z. M. Younossi, "Oral L-ornithine-L-aspartate improves health-related quality of life in cirrhotic patients with hepatic encephalopathy:An open-label, prospective,multicentre observational study,"ClinicalDrug Investigation, vol. 31, no. 4, pp. 213– 220, 2011.
7. N. M. Bass, K. D. Mullen, A. Sanyal et al., "Rifaximin treatment in hepatic encephalopathy," The New England Journal of Medicine, vol. 362, no. 12, pp. 1071–1081, 2010.
8. G. Garcia-Tsao, A. J. Sanyal, N. D. Grace et al., "Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis," Hepatology, vol. 46, no. 3, pp. 922– 938, 2007.
9. J.Wen, Q. Liu, J. Song, M. Tong, L. Peng, and H. Liang, "Lactulose is highly potential in prophylaxis of hepatic encephalopathy in patients with cirrhosis and upper gastrointestinal bleeding: Results of a controlled randomized trial," Digestion, vol. 87, no. 2, pp. 132–138, 2013.
10. P. Sharma, A. Agrawal, B. C. Sharma, and S. K. Sarin, "Prophylaxis of hepatic encephalopathy in acute variceal bleed: A randomized controlled trial of lactulose versus no lactulose," Journal of Gastroenterology and Hepatology, vol. 26, no. 6, pp. 996–1003, 2011.
11. Higuera-de-la-Tijera , Servín-Caamaño AI, Salas-Gordillo F, Pérez-Hernández JL, Abdo-Francis JM, Camacho-Aguilera J . et al. Primary Prophylaxis to Prevent the Development of Hepatic Encephalopathy in Cirrhotic Patients with Acute Variceal Bleeding. Can J Gastroenterol Hepatol. 2018 Jul 10;2018:3015891.

Prepared by Pharm D student: Tala Al-Gharram
Supervised by clinical pharmacist: Eshraq Al-Abween