Pharmacotherapies that Specifically Target Ammonia for the Prevention and Treatment of Hepatic Encephalopathy in Adults with Cirrhosis

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BACKGROUND: Ammonia plays a key role in the genesis of hepatic encephalopathy (HE). Recent interest has focused on drugs which specifically target ammonia, e.g. sodium benzoate (SB), glycerol phenylbutyrate (GPB), ornithine phenylacetate (OP), AST-120, and polyethylene glycol (PEG). This study aims to evaluate the utility of these pharmacotherapies vs. placebo or non-absorbable disaccharides (NAD), for the management of HE in people with cirrhosis. L-ornithine L-aspartate is not included.
METHODS: Electronic/manual searches of the literature were undertaken for relevant RCTs. The results of the meta-analyses are presented as risk ratios (RR) or mean differences (MD) with 95% confidence intervals (CIs). Bias control was assessed using the CHBG domains and the certainty of the evidence using GRADE.

RESULTS: Eleven RCTs were identified involving SB (n =1), GPB (n =1), OA (n =2), AST-120 (n=52) and PEG (n =3). Treatment periods ranged from five days to 16 weeks. All but one trial was at high risk of bias; the certainty of the evidence was very low for all outcomes. Nine trials, with 733 participants, reported blood ammonia concentrations. Significant reductions were observed in placebo-controlled trials evaluating SB (MD 232.00, 95% CI 246.85 to 217.15); GPB (MD 212.00, 95% CI 223.37 to 20.63); OP (MD 227.10, 95% CI 248.55 to 25.65) and AST-120 (MD 222.00, 95% CI 226.75 to 217.25). No significant differences in blood ammonia concentrations were observed when compared to NADs. Eleven trials, with 943 participants, reported mortality data, although there were no events in five trials. No beneficial or harmful effects were found in any of the trials. Seven trials, with 521 participants reported data on HE. Beneficial effects were identified for GPB vs. placebo (RR 0.57, 95% CI 0.36 to 0.90; 178 participants; 1 trial; NNTB = 6) and for PEG vs. lactulose (RR 0.19, 95% CI 0.08 to 0.44; 190 participants; 3 trials; NNTB = 4); no beneficial effects were observed in the remaining three trials with extractable data (Figure 1). Ten trials, with 790 participants, reported a total of 130 serious adverse events. There was no evidence of beneficial or harmful effects of the five agents when compared to placebo or NADs.

CONCLUSIONS: These agents generally reduce blood ammonia concentrations, when compared to placebo, but not when compared to NADs. Their overall effects on clinical outcomes of interest and the potential harms associated with their use remain uncertain. Further evidence is needed to fully evaluate their utility in this clinical setting.

Figure 1: Effect of treatments which specifically target ammonia on hepatic encephalopathy in cirrhosis