Bye Bye Benzoate: What Next for Hyperammonemia in Liver Disease?

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See ''Efficacy and Safety of Sodium Benzoate in The Management of Hyperammonemia in Decompensated Chronic Liver Disease of the Childhood—A Double-blind Randomized Controlled Trial'' by Snehavardhan et al on page 165.

Hepatic encephalopathy (HE) is a serious, and often under recognized, complication of childhood liver disease (1). HE has an obvious impact on quality of life and educational achievement in childhood. Clinical experience suggests it is likely to have a negative impact on survival in childhood as has been proven in adults (2). In addition, evidence in adult practice shows we cannot be blasé about its complete reversibility after transplantation (3), emphasizing the importance of prompt recognition and treatment.

The pathogenesis of HE is not completely understood but there is a strong association with elevated ammonia levels (1,2). Ammonia is an established neurotoxin and the degree and duration of hyperammonemia is strongly predictive of poor developmental outcome in children with urea cycle disorders (UCD) (4). In UCD, the aim is to keep venous ammonia less than 80 μmol in order to maximize neurologic potential. These targets may not be applicable in HE where other noxious factors contribute to the clinical picture including, but not limited to, mercaptans, short-chain fatty acids and inflammatory cytokines. Given these uncertainties, it is probably best that ammonia is only monitored where HE is present, or strongly suspected, as elevated ammonia and HE are not synonymous.

Notwithstanding this, established therapy for HE appears to work by reducing plasma ammonia. The standard of care for HE, after identification and treatment of any precipitating factor(s), includes lactulose and nonabsorbed antibiotics. A common clinical dilemma is what to do next when these measures are insufficient or not tolerable. Sodium benzoate has long been used successfully to lower ammonia in children with UCD through promoting nitrogen loss (4). Sodium benzoate conjugates with the amino acid glycine in liver mitochondria to form Hippurate, which is then rapidly renally excreted. In theory, this alternate pathway could be effective in HE, but it is unclear if sodium benzoate would undergo conjugation in the presence of severe liver disease and it represents a significant extra sodium load. Limited data suggests that sodium benzoate may be as effective as lactulose in HE in adults with chronic liver disease (5) but it has not been evaluated in pediatric liver disease until now.

In this issue, Snehavardhan et al (6) describe the remarkable achievement of a randomized controlled trial of sodium benzoate to treat hyperammonemia and HE in children with decompensated chronic liver disease. Children with hyperammonemia were randomized to receive sodium benzoate or placebo in addition to standard-of-care therapy, with the primary endpoint being reduction in plasma ammonia after 5 days. Sodium benzoate was given orally and in nonconventional dosing, with a larger loading dose and lower maintenance dose than normally used in the treatment of UCD. They found that ammonia fell equally with both regimens over the 5 days of the study but sodium benzoate lowered ammonia more rapidly in the first 48 hours. Sodium benzoate had no effect on resolution of HE, overall survival, time to discharge and was associated with a trend to increased ascites. Tragically, nearly 30% of these children subsequently died awaiting liver transplantation.

So what have we learned? Firstly, we can be reassured that conventional standard of care for HE with lactulose and rifaximin seems effective in the short-term.

Secondly, it has shown that sodium benzoate can lower ammonia in end-stage pediatric liver disease. The effect, however, is temporary and compromised by the risk of fluid overload. The rapid fall in plasma ammonia after the large loading dose suggests that higher maintenance doses of sodium benzoate might be more effective, but these are unlikely to be tolerable. Thirdly, this study confirms the appalling outlook of decompensated pediatric liver disease without liver transplantation.

The overall negative result should not diminish the significance and importance of this study, which has brought some objectivity to an important issue in a very ill group of children. The challenge for the pediatric hepatology community will be how to build on this team's work and to plan the next randomized trial in HE. These results suggest that sodium benzoate is not an attractive candidate going forward, but other potential agents exist. Sodium phenylbutyrate also promotes alternate pathway nitrogen excretion, in this case by conjugation with glutamine. It is as effective as sodium benzoate for hyperammonemia but with a smaller sodium load (7). Another exciting option is L-ornithine L-aspartate (LOLA). LOLA stimulates urea cycle activity, promoting urea excretion while also increasing muscle glutamine synthesis from Ammonia. It has been shown to be well tolerated and effective at reducing hyperammonemia and HE in adult practice as an add-on to standard-of-care treatment (8). Let us hope these agents can be tested in future pediatric randomized trials.

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