Novel Ammonia-Lowering Agents for Hepatic Encephalopathy

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KEYWORDS

• AST-120 • Cirrhosis • Glycerol phenylbutyrate • MARS • Ornithine phenylacetate • Benzoate • Polyethylene glycol • PEG

KEY POINTS

- Glycerol phenylbutyrate (GPB) decreases the likelihood of being hospitalized for hepatic encephalopathy (HE) or experiencing an overall hepatic encephalopathy event compared with placebo.
- Ornithine phenylacetate (OP) enhances the excretion of ammonia in the urine as phenylacetylglutamine (PAGN); a phase IIb trial is currently investigating its use for acute HE.
- Polyethylene glycol (PEG) seems an effective alternative to treat acute HE (compared with lactulose), with a potential to decrease hospital length of stay.

INTRODUCTION

Hepatic encephalopathy (HE) is a common and devastating complication of cirrhosis. The spectrum of HE ranges from covert HE (previously termed minimal HE) to overt HE (previously termed acute HE) and accounts for frequent hospitalization, decrease in the quality of life, and poorer outcomes than in cirrhotic patients who have not had HE.

Although it is long been believed that ammonia produced by gut bacteria is an important contributing factor to the pathogenesis of HE, HE is a multifactorial disease (**Fig. 1**) process for which the underlying mechanisms leading to altered cerebral function are still not well understood.[1] The production of ammonia can arise from gram-negative anaerobes (ie, *Enterobacteriaceae*, *Proteus*, and *Clostridium* species) that have bacterial urease, converting urea from the blood into ammonia and carbon dioxide.[2–4] One of the purported mechanisms of action for lactulose is that it helps clear

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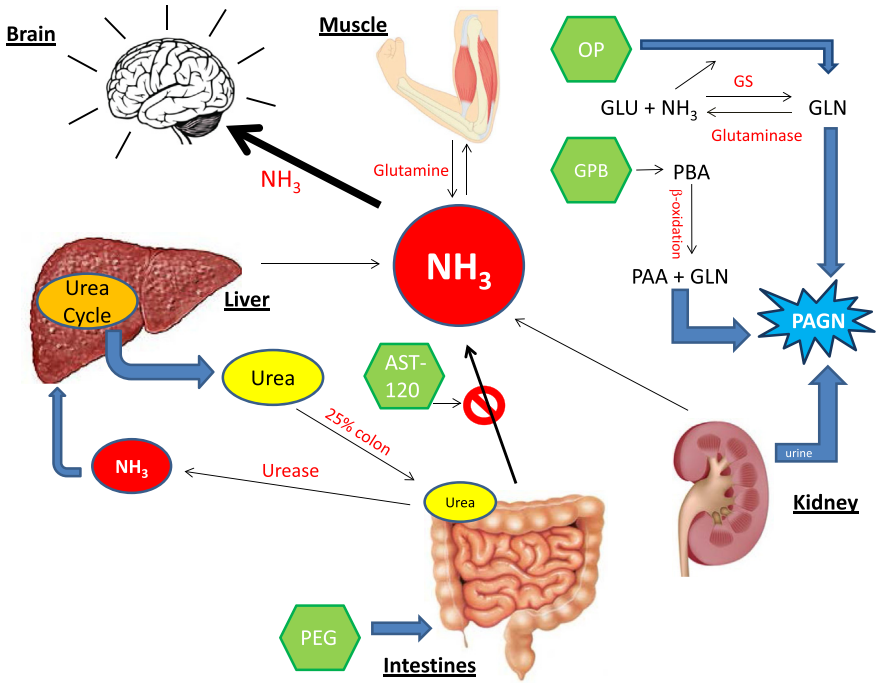

Fig. 1. Multiorgan ammonia (NH_3) pathways with specific NH_3-lowering medications used in cirrhosis. Circulating concentrations of NH_3 are shown with multiorgan involvement in the production of NH_3, ultimately resulting in NH_3 crossing the blood-brain barrier, contributing to astrocyte swelling and HE, because decreased urea cycle capability and reduced liver glutamine synthetase (GS) activity is present in cirrhosis. The alternative pathway is shown at the top, where NH_3 binds with glutamate (GLU)-forming glutamine (GLN) after enzymatic processing using GS. Both ornithine phenylacetate (OP) and glycerol phenylbutyrate (GPB) are NH_3-lowering medications; they combine GLN and phenylacetate (PAA) to form phenylacetylglutamine (PAGN), which is excreted in the urine. AST-120 is a carbon microsphere adsorbent, which binds NH_3 in the gut, thus lowering circulating NH_3 levels. Polyethylene glycol (PEG) is a cathartic, which causes rapid clearance of gut bacterial synthesizing NH_3 to be excreted into the feces. Approximately one-fourth of urea-derived byproducts from the urea cycle is shunted to the colon (not shown; remaining three-fourths of urea excreted in the kidneys), where urease-producing bacterial organisms produce NH_3 that enters the portal circulation. Skeletal muscle also contributes in the regulation of NH_3, as depicted. Not shown is the presence of GS and glutaminase in each organ, contributing to NH_3 homeostasis. PBA, phenylbutyric acid. NH3 circles represent circulating ammonia.

the GI tract of ammonia producing bacteria. Additionally, enterocytes in the small bowel seem to generate ammonia via intestinal glutaminase, an enzyme that metabolizes glutamine into glutamate and ammonia[5,6] and is found up-regulated in cirrhotic patients with minimal and overt HE.[7,8] Additionally, because the ability of the liver to clear ammonia is diminished in cirrhosis, and because portal hypertension leads to shunting of blood around the sinusoids, cirrhosis leads to hyperammonemia. The ensuing elevation in ammonia is thought to cause oxidative dysfunction in the mitochondria of astrocytes, resulting in cerebral edema and neurologic dysfunction.[9] Regardless of the precise mechanism of hyperammonemia, because it is thought to be a major underlying mechanism contributing to the development of HE, this review focuses on novel ammonia-lowering approaches in HE.