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Secondary Ammonia Scavenge With Glycerol Phenylbutyrate Improves Hyperammonemia Following Portosystemic Shunting

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Abstract: Portosystemic shunts are used to treat portal hypertension arising from extrahepatic portal venous obstruction. They decompress the portal system by allowing intestinal blood to bypass the liver and enter directly into the systemic circulation. These shunts increase the risk of minimal hepatic encephalopathy and altered neurodevelopmental outcomes in affected children. Treatment options are limited and have been extrapolated from those used in cirrhosis. We describe the use of glycerol phenylbutyrate as an alternate management strategy. A 3-year-old boy underwent distal splenorenal shunt for refractory variceal bleeding secondary to portal hypertension. He had neurologic deterioration and hyperammonemia refractory to traditional management strategies. Glycerol phenylbutyrate was initiated and resulted in a sustained improvement in ammonia levels, behavior, and school performance. This case illustrates the successful use of glycerol phenylbutyrate in a noncirrhotic patient with Portosystemic shunt and minimal hepatic encephalopathy refractory to conventional management strategies.

Key Words: hepatic encephalopathy, minimal hepatic encephalopathy

INTRODUCTION

Portosystemic shunts (PSSs) decompress the portal system by allowing intestinal blood to bypass the liver and enter directly into the systemic circulation. Unfortunately, these shunts predispose children to minimal hepatic encephalopathy (MHE) and altered neurodevelopmental outcomes (1). Treatment options for MHE are limited and have been extrapolated from those used in the context of cirrhosis (2). In this report, we describe the use of glycerol phenylbutyrate as an alternate therapy for a patient with MHE refractory to conventional management strategies.

CASE REPORT

A 3-year-old boy underwent distal splenorenal shunt for refractory variceal bleeding secondary to portal hypertension. His medical history was significant for preterm delivery at 33 weeks gestational age and umbilical catheterization in the neonatal intensive care unit. The cause of his portal hypertension was extrahepatic venous obstruction with cavernous transformation of the portal vein, identified on ultrasound and magnetic resonance imaging. He was not a candidate for a Rex shunt due to thrombosis of his left portal vein. One month postoperatively, he developed suspected MHE (ammonia level 54 μmol/L) and was treated empirically with lactulose. His clinical status worsened with behavioral changes and sleep disturbance (ammonia levels ranging from 80 to 100 μmol/L). He presented to the emergency department with acute neurologic decompensation and an ammonia level of 148 μmol/L. Lactulose dosing was increased and rifaximin (200 mg PO BID) was added to the treatment regimen.

The patient had persistent behavioral concerns over the ensuing 12 months which led to additional treatment measures including cycling rifaximin with lactulose, initiation of a vegan diet, dietetic review to ensure there was no caloric deficit to precipitate catabolism, and a seven-strain probiotic to promote low urease producing strains of bacteria. Analysis of his serum amino acid profile was normal except for low branched-chain amino acids reflecting reduced dietary protein intake as the intestinal venous drainage bypassed the liver via the PSS. We did not find any evidence of a urea cycle disorder using plasma amino acids, urine amino acids, urine orotic acid, ornithine transcarbamylase gene sequencing and multiplex ligation-dependent probe amplification (MLPA). However, his hyperammonemia proved refractory to dietary changes, antibiotic therapies, probiotics and lactulose. He had recurrent symptomatic hyperammonemia with serum ammonia levels exceeding 100 μmol/L during three discrete episodes.

Glycerol phenylbutyrate was initiated at a dose of 2.5 mL by mouth TID (11 mL/m^2 and 12.1 g/m^2), and subsequently reduced to a maintenance dose of 1.8 mL by mouth TID (8 mL/m^2 and 8.8 g/m^2). On this therapy, there has been a sustained stabilization of serum ammonia levels, with a pretreatment median of 64.0 μmol/L (IQR 49.0–81.0) compared to a post-treatment median of 55.0 μmol/L (IQR 45.0–68.5) (P = 0.0268, Fig. 1). Following the introduction of glycerol phenylbutyrate, there were three occasions during which the serum ammonia level was >100 μmol/L. These were not felt to be clinically significant and rather spurious as they were not associated with clinical symptoms and normalized without intervention within 24 hours.

This has corresponded to a marked and sustained change in his behavior, improvement in his ability to concentrate, school performance, fine motor skills, and no further presentations of hyperammonemic encephalopathy. He has had no HE events in 24 months following initiation of glycerol phenylbutryrate. His amino acid profile remains unchanged.

DISCUSSION

Although the pathogenesis of HE is not entirely understood, hyperammonemia is considered to be an important factor and correlated with symptoms in our patient. Ammonia is produced from dietary protein catabolism, with subsequent conversion to urea in the

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The parent and legal guardian of the patient presented in this case report provided informed consent and were aware of the intent to publish and agree to it.

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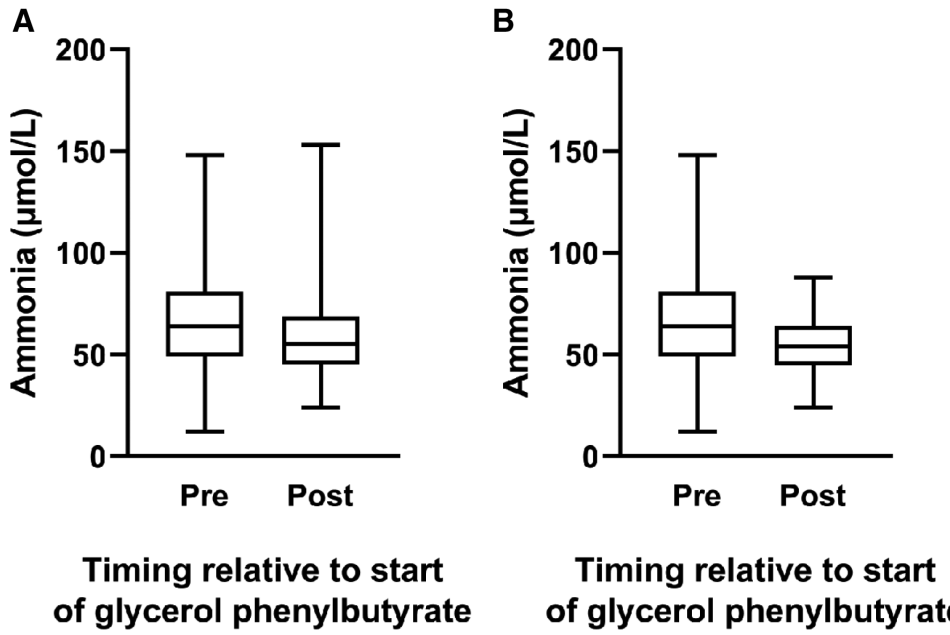

FIGURE 1. Box plot demonstrating median ammonia values and interquartile ranges before and following initiation of glycerol phenylbutyrate. A) including spurious ammonia values exceeding 100 µmol/L on three occasions post glycerol phenylbutyrate. B) excluding spurious ammonia values exceeding 100 µmol/L on 3 occasions post glycerol phenylbutyrate.

urea cycle. In the presence of a PSS, blood flow bypasses the liver and therefore a crucial step in dietary ammonia detoxification (3). With this type of shunt and portal vein obstruction, ammonia derived from dietary protein deamination enters the systemic circulation without first undergoing detoxification by periportal hepatocytes. This results in the risk of systemic exposure to hyperammonemia despite the absence of a urea cycle disorder.

Glycerol phenylbutyrate is an oral medication typically used in the treatment of urea cycle disorders by using a scavenger pathway to detoxify ammonia. After ingestion, the prodrug is acted on by pancreatic lipases in the intestinal lumen producing phenylbutyrate, which is absorbed into the circulation. Phenylbutyrate will subsequently undergo beta-oxidation and be converted to phenylacetate then phenylacetyl-CoEnzyme A. Conjugation with glutamine, which contains two molecules of nitrogen, yields phenacetylglutamine. This is water-soluble and excreted in the urine thereby providing a secondary pathway for elimination of ammonia. Because the conjugation can occur in the circulation, our aim was to reduce prehepatic ammonia levels in the systemic circulation using a non-urea cycle pathway for renal excretion of nitrogenous waste (4). This approach has been shown to reduce HE events and ammonia levels in patients with cirrhosis (5). This case illustrates the successful use of glycerol phenylbutyrate in a noncirrhotic patient with PSS and MHE refractory to conventional management strategies. Our experience provides further evidence for its use in this patient population in whom uncontrolled hyperammonemia can have a significant negative impact on daily functioning and long-term cognitive outcomes.

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