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Document Details

Source : Mol Genet Metab

Volume : 102

Issue : 3

Date : 2011 Mar

Pages : 276-277

Author : Diaz GA, et al

Title : Phase 3 Blinded, Randomized, Crossover Comparison of Sodium Phenylbutyrate (NaPBA) and Glycerol Phenylbutyrate (GPB): Ammonia (NH3) Control in Adults with Urea Cycle Disorders (UCDs)

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was referred for a metabolic evaluation. At the time she presented to care, there was no evidence of protein aversion, ophthalmologic findings, or neurologic involvement. The patient was pregnant with a fetus measuring at 7 weeks of gestation at the time of her initial metabolic evaluation.

Results: At presentation, an acylcarnitine profile revealed an elevated Propionyl carnitine (C3) level of 1.84 (reference range 0–1.60), total Hcy level of 56.18 (reference range of 10.50–16.7 μmol/L) and 205 mg/g creatinine of MMA measured in urine organic acid analysis. Molecular genetic sequencing of the *MMACHC* gene revealed two missense mutations [c.388T>C (p.Y130H), c.643T>C (p.Y215H)] consistent with the biochemical diagnosis of Cbl C deficiency.

The patient was treated with 1 mg of intramuscular hydroxocobalamin per week. After one dose of hydroxocobalamin, her total Hcy level decreased from a level of 56.18 μmol/L to a level of 37.71 μmol/L and her MMA level decreased from a level of 205 mg/g creatinine to a level of 150 mg/g creatinine. She remained on a weekly regimen of hydroxocobalamin and her metabolites quickly normalized and remained within normal limits throughout the pregnancy. The patient delivered a health child following a full term pregnancy without complications.

Conclusion: The attenuated phenotype of Cbl C deficiency may not be apparent in early adulthood. The late onset form of Cbl C deficiency may respond well to therapeutic treatment with hydroxocobalamin and treatment is able to normalize metabolites throughout pregnancy. The association between elevated total Hcy levels and increased risk for spontaneous abortions is not well delineated and should be studied further.

25) Phase 3 blinded, randomized, crossover comparison of sodium phenylbutyrate (NaPBA) and glycerol phenylbutyrate (GPB): Ammonia (NH_3) control in adults with urea cycle disorders (UCDS)

GA Diaz[1], J Bartley[2], N Longo[3], W Berquist[4], A Feigenbaum[5], R Gallagher[6], W Rhead[7], D Bartholomew[8], CO Harding[9], MS Korson[10], U Lichter-Konecki[11], SA Berry[12], W Smith[13], SE McCandless[14], J Vockley[15], S Bart[16], D Kronn[17], R Zori[18], Sandesh Sreenath-Nagamani[22], M Summar[11], C Jomphe[19], M Beliveau[19], J Mauney[20], K Dickinson[21], M Mokhtarani[21], D Coakley[21], BF Scharschmidt[21], B Lee[22]

[1]*Mt. Sinai School of Medicine, NY, NY, USA*
[2]*Long Beach, CA, USA*
[3]*Univ of UT, Salt Lake City, UT, USA*
[4]*Stanford, Palo Alto, CA, USA*
[5]*Hospital for Sick Children, Toronto, Ontario, Canada*
[6]*Denver Children's Hospital, Denver, CO, USA*
[7]*Med College of WI, Milwaukee, WI, USA*
[8]*Nationwide Children's Hospital, Columbus, OH, USA*
[9]*Oregon Health & Sciences Univ., Portland, OR, USA*
[10]*Tufts Medical Center, Boston, MA, USA*
[11]*Children's National Medical Center, Washington, DC, USA*
[12]*Univ of MN, Minneapolis, MN, USA*
[13]*Maine Medical Ctr., Portland, ME, USA*
[14]*UHCMC and CWRU, Cleveland, OH, USA*
[15]*Univ of Pittsburgh, Pittsburgh, PA, USA*
[16]*SNBL, Baltimore MD, USA*
[17]*Westchester Medical Ctr., Westchester, NY, USA*
[18]*Univ of FL, Gainesville, FL, USA*
[19]*Pharsight Corp., Montreal, Quebec, Canada*
[20]*Chiltern, Wilmington NC, USA*
[21]*Hyperion Therapeutics, Inc., South San Francisco, CA, USA*
[22]*Baylor College of Medicine, HHMI, Houston, TX, USA*

Glycerol phenylbutyrate (GPB, also referred to as GT4P or HPN-100) is being developed as a treatment alternative to sodium phenylbutyrate (NaPBA) for UCD patients. Both drugs mediate waste nitrogen scavenging through conjugation of phenylacetic acid (PAA, derived from phenylbutyric acid [PBA]) with glutamine to form phenylacetylglutamine (PAGN) which is excreted in the urine. GPB is a short chain triglyceride (liquid) and 5.8 mL TID is anticipated to be the equivalent of 40 tablets (20 g) of NaPBA.

Study design: Protocol HPN-100-006 was a 4-week randomized, blinded, cross-over comparison of the NaPBA with a PBA-equimolar GPB dose to establish non-inferiority of GPB to NaPBA in NH_3 control. Subjects underwent 24-h blood sampling for NH_3 and PK after each two week treatment period.

Results: 46 subjects (41 OTC, 3 ASS, and 2 CPS) were randomized; 45 received at least one dose of study drug and constituted the ITT population; 44 completed the study. Subjects were evenly distributed between treatment arms, had been taking NaPBA for an average of ~13 yr and received an average dose of 13.95 g/day (7.8 g/m^2/day) of NaPBA and 13.49 g/day (7.55 g/m^2/day) of GPB while on study. NH_3 values on both drugs were lowest after overnight fasting and peaked postprandially. 95% confidence intervals for NH_3 (24 h AUC) on GPB relative to NaPBA in the ITT population (0.799, 1.034) were below the predefined non-inferiority margin of 1.25; mean NH_3 levels on GPB were ~10% lower than on NaPBA (34.7 vs. 38.4 μmol/L; not significant). Glutamine was lower on GPB than NaPBA (758 vs. 809 μmol/L; ULN = 746; $p<0.05$) by post-hoc analysis. At baseline, 91% of patients reported ≥1 organ system complaint with GI (56%) most common. AEs on study were reported by 61% and 51% of subjects during GPB and NaPBA treatment, respectively, with most being GI and generally mild. No clinically significant lab or ECG changes were observed. One subject experienced a hyperammonemic crisis and one withdrew early because of high NH_3 and headache; both were on

NaPBA. One subject had an SAE of gastroenteritis on GPB judged unrelated. As compared with NaPBA, 24-hour AUC and peak plasma PAA levels were significantly lower on GPB, trough values higher, and overall 24 h urinary PAGN output identical but with more even day/night distribution.

Conclusions: This pivotal trial demonstrated non-inferiority of GPB to NaPBA for NH_3 control. The authors theorize that the PK findings and trend toward lower NH_3 and glutamine observed in the pivotal study may be explained by slower GI absorption of PBA when delivered as a triglyceride (GPB) rather than a salt (NaPBA), leading to higher trough levels of the active moiety, PAA. The data also support the utility of urinary PAGN as a clinically useful biomarker.

26) Natural history study of very-long-chain Acyl-CoA dehydrogenase deficiency in The Netherlands

E.F.Diekman [1], P. Vellekoop [1], R.J.A. Wanders [2], H.R. Waterham [2] H de Klerk [3], G.P.A. Smit [4], M de Vries [5], M.F.Mulder [6], G.Visser [1]

[1]*UMCU Utrecht, The Netherlands*
[2]*AMC Amsterdam, The Netherlands*
[3]*Erasmus MC Rotterdam, The Netherlands*
[4]*UMCG Groningen, The Netherlands*
[5]*Radboud MC Nijmegen, The Netherlands*
[6]*VUmc Amsterdam, The Netherlands*

Background: Since 2007 Very Long Chain Acyl-CoA Dehydrogenase Deficiency (VLCADD) is included in the Dutch neonatal screening program (NSP). Evidence based guidelines for treatment and follow-up of patients detected by the NSP are crucial to sustain proper care after neonatal diagnosis. For VLCADD, however, these guidelines have remained ill-defined.

VLCADD is a rare disorder affecting the mitochondrial beta-oxidation of long-chain fatty acids. Clinical symptoms arise, or are exacerbated during catabolic situations e.g. during illness or fasting. Organs most frequently involved are those using long-chain fatty acids as primary energy source, such as the heart and skeletal muscles. Age at onset, manifestation patterns and clinical severity differ between patients.

Currently in the Netherlands dietary measures aimed at preventing catabolism are the only available treatment option for patients with VLCADD. Long term outcome of these measures is unknown. There is a serious lack of historical controls. In order to be able to evaluate the true yield of the NSP, those historical controls are, however, of the utmost importance.

Goal: To gain insight into incidence, clinical presentation and treatment of VLCADD in the Netherlands.

Methods: Retrospective study. Patients were searched for by contacting clinical metabolic centers; metabolic laboratories specialized in VLCADD diagnostics, patient organizations and the Dutch Diagnosis Registration Metabolic Diseases (www.ddrmd.nl). Patient data were collected by patient file analysis using a standardized protocol.

Results: Thirty patients were identified including 21 males and 9 females, born between 1963 and 2010. Seven patients were identified by newborn screening; including one severely affected, two mildly affected and four are asymptomatic, at least until now. A broad spectrum of mutations was found of which c.848T>C (p.V283A) was found most frequently. Generally no complications were reported during pregnancy or birth. Symptoms most frequently reported in childhood were hypoglycemia, muscular pains and cramps accompanied by increased plasma creatine kinase (CK) levels, and hepatomegaly. In adulthood muscular complaints and severely impaired daily functioning were most prominent. All patients are treated with dietary measures varying from LCT restriction, MCT enrichment, fatty acid supplementation and tube feeding, to carbohydrate or MCT intake before exercise. Treatment with a LCT restricted, MCT enriched diet appears to be effective in short-term disease control. In some adult patients severe impairment of daily functioning despite dietary treatment was reported.

Conclusions: Since the introduction of the NSP, more patients with VLCADD have been identified as previously (est. incidence before screening 1:300,000, after 1:80,000). It is not yet clear whether asymptomatic VLCADD is relatively common but under-diagnosed, or whether a significant portion of infants detected by NSP might never become symptomatic unless experiencing significant catabolic stress. Factors predicting disease course (genotype, enzyme activity, CK, e.o.) and the effects of screening and (early) treatment on long-term outcome have to be determined to gain more insight. We will perform structured follow-up of all identified patients in an expertise centre for metabolic diseases.

27) Metabolic predictors of coagulation abnormalities in glycogen storage disease type 1

Areeg H. El-Gharbawy[1], Courtney D. Thornburg[2], Stephanie Austin[1], Priya S. Kishnani[1]

[1]*Department of Pediatrics, Division of Medical Genetics, Duke University Medical Center, Durham, NC, USA*
[2]*Department of Pediatrics, Division of Hematology/Oncology, Duke University Medical Center, Durham, NC, USA*

Background: Glycogen storage disease type 1(GSD1) is an inborn error of metabolism caused by defective glucose-6-phosphatase complex. Enzymatic deficiency leads to fasting hypoglycemia, hyperlactatemia, hyperuricemia, and hyperlipidemia. Acquired platelet dysfunction and reduced von Willebrand factor (VWF) have been described in patients with poorly controlled GSD1. The coagulation defects manifest as epistaxis, easy bruising and bleeding during surgical procedures. While, dietary intervention reportedly abrogates the bleeding diathesis, it is unknown if there is a specific metabolic factor which accounts for the laboratory abnormalities and clinical symptoms.

Objectives: To evaluate the relationship between predictors of metabolic control and platelet aggregation and VWF in patients with GSD1.