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ELEVATED PHENYLACETIC ACID LEVELS DO NOT CORRELATE WITH ADVERSE EVENTS IN PATIENTS WITH UREA CYCLE DISORDERS OR HEPATIC ENCEPHALOPATHY AND CAN BE PREDICTED BASED ON THE PLASMA PAA TO PAGN RATIO

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Abstract

Background—Phenylacetic acid (PAA) is the active moiety in sodium phenylbutyrate (NaPBA) and glycerol phenylbutyrate (GPB, HPN-100), both are approved for treatment of urea cycle disorders (UCDs) - rare genetic disorders characterized by hyperammonemia. PAA is conjugated with glutamine in the liver to form phenylacetyleglutamine (PAGN), which is excreted in urine. PAA plasma levels ≥500 μg/dL have been reported to be associated with reversible neurological adverse events (AEs) in cancer patients receiving PAA intravenously. Therefore, we have investigated the relationship between PAA levels and neurological AEs in patients treated with these PAA pro-drugs as well as approaches to identifying patients most likely to experience high PAA levels.

Methods—The relationship between nervous system AEs, PAA levels and the ratio of plasma PAA to PAGN were examined in 4683 blood samples taken serially from: [1] healthy adults [2], UCD patients ≥2 months of age, and [3] patients with cirrhosis and hepatic encephalopathy (HE). The plasma ratio of PAA to PAGN was analyzed with respect to its utility in identifying patients at risk of high PAA values.

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Results—Only 0.2% (11) of 4683 samples exceeded 500 ug/ml. There was no relationship between neurological AEs and PAA levels in UCD or HE patients, but transient AEs including headache and nausea that correlated with PAA levels were observed in healthy adults. Irrespective of population, a curvilinear relationship was observed between PAA levels and the plasma PAA:PAGN ratio, and a ratio > 2.5 (both in μg/mL) in a random blood draw identified patients at risk for PAA levels > 500 μg/ml.

Conclusions—The presence of a relationship between PAA levels and reversible AEs in healthy adults but not in UCD or HE patients may reflect intrinsic differences among the populations and/or metabolic adaptation with continued dosing. The plasma PAA:PAGN ratio is a functional measure of the rate of PAA metabolism and represents a useful dosing biomarker.

Keywords

BUPHENYL; glycerol phenylbutyrate; HPN-100; neurological adverse events; pharmacokinetics; RAVICTI; sodium phenylbutyrate

INTRODUCTION

Glycerol phenylbutyrate, a sodium- and sugar-free phenylbutyrate derivative, and sodium phenylbutyrate are approved as ammonia lowering agents in patients with urea cycle disorders (UCDs). Both are pro-drugs of phenylacetic acid (PAA), which is formed by beta-oxidation from phenylbutyric acid (PBA) delivered either as glycerol phenylbutyrate following its intestinal hydrolysis by pancreatic lipases [1] or as sodium phenylbutyrate following dissociation in the stomach. PAA is conjugated with glutamine by glutamine-N-phenylacetyltransferase, largely in the liver and to a lesser extent in the kidney [2], to form phenylacetylglutamine (PAGN), which is excreted in urine, thereby providing an alternate pathway to urea for waste nitrogen excretion. In controlled studies population pharmacokinetic analyses of sodium phenylbutyrate and glycerol phenylbutyrate, it has been shown that the gastrointestinal absorption of PBA is approximately 75% slower when delivered as glycerol phenylbutyrate vs. sodium phenylbutyrate and that plasma PAA and PAGN levels show less variability during glycerol phenylbutyrate dosing. [3]-[7]. There are over 30 reports of the administration of sodium phenylacetate or sodium phenylbutyrate to healthy volunteers, patients with UCDs or other metabolic disorders and patients with cancer, many of which reported some adverse events (AEs) attributed to PAA (Supplemental Table 1) [8]-[36]. These reversible AEs in cancer patients were reported in studies involving continuous or intermittent intravenous administration designed to maintain high levels of PAA, suggesting that duration of exposure as well as peak PAA levels are important [35],[3].

The AEs reportedly associated with high levels of PAA have most commonly included nausea, headache, emesis, fatigue, weakness, lethargy, somnolence, dizziness, slurred speech, memory loss, confusion, and disorientation [35], [36]. Except for the symptoms of Kussmaul respiration, metabolic acidosis, cerebral edema, and coma associated with a fatal overdose of sodium phenylacetate/sodium benzoate (AMMONUL®)[13], the symptoms were rapidly reversible with reduced dosing or interruption of dosing.

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Based on a detailed analysis of the timing of the AEs in relation to blood PAA concentrations, Simell calculated the safe upper PAA concentration limit to be 3.5 mmol/L, equivalent to 476 μg/mL [22], and Thibault reported that AEs were associated with PAA levels ranging from 499–1285 μg/mL [35], [36] .

Sodium phenylbutyrate (BUPHENYL®) has been used for over three decades in the treatment of UCDs. Despite the fact that the AEs reportedly associated with elevated plasma PAA levels can mimic those associated with hyperammonemia, little is known regarding the relationship between PAA levels and AEs in UCD patients. The clinical trials of glycerol phenylbutyrate (RAVICTI®, HPN-100), which included over 100 UCD patients, 80 of whom underwent comparative study of sodium phenylbutyrate and glycerol phenylbutyrate [3] - [6] (the largest prospectively studied group of patients with this rare disorder), 193 patients with advanced cirrhosis complicated by hepatic encephalopathy (HE) [37], and more than 90 healthy adult subjects have afforded a unique dataset and opportunity to systematically examine the relationship between PAA levels and AEs and to explore biomarkers indicative of patients most likely to experience elevated PAA levels.

METHODS

Clinical Studies (Table 1)

Data from a thorough QTc study in healthy adults, five clinical studies in UCD patients and an open label safety and dose escalation study as well as a randomized, double-blinded controlled phase 2 study of patients with decompensated cirrhosis complicated by HE formed the basis for these analyses.

UCD Patients

Eighty UCD patients completed 4 short-term (10 to 28 days) cross-over studies of sodium phenylbutyrate vs. glycerol phenylbutyrate (Table 1). The short-term UCD study population included 26 pediatric patients ages ≥2 mos through 17 years who received a mean (range) dose of 8 (1-19) g/day of glycerol phenylbutyrate or an equivalent dose of sodium phenylbutyrate and 54 adults patients ages 18 years or older who received a mean (range) dose of 13 (2-34) g/day of glycerol phenylbutyrate or an equivalent dose of sodium phenylbutyrate [3] [4] [5][6]. In addition, data from 100 UCD patients enrolled in 12-month glycerol phenylbutyrate treatment protocols including 49 children and 51 adults were analyzed in relation to PAA levels over time and the occurrence of the symptoms reported in cancer patients by Thibault [35][36][4] [5][6] during 12 months treatment.

Patients with Cirrhosis and HE

Data from a 4-week safety and dose escalation study and a multicenter, randomized placebo-controlled study of 178 patients with cirrhosis and hepatic encephalopathy who received 13.2 g/day of glycerol phenylbutyrate (N=90) or placebo (N=88) for 16 weeks were analyzed [37], [38] (Table 1). Patients were monitored for safety and frequent PK samples were taken over the course of the study.

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Healthy Adults

A total of 98 healthy adults (mean age of 28; 53 male 45 female) participated in a blinded, randomized, cross over study to assess effects of glycerol phenylbutyrate and its metabolites on QTc and other ECG parameters (Table 1). In this protocol 12 subjects received 29.7 g/day, 4 subjects 39.6 g/day of glycerol phenylbutyrate and 68 subjects received placebo, moxifloxacin as the positive control and glycerol phenylbutyrate at doses of 13.2 g/day and 19.8 g/day administered three times daily for 3 days.

Adverse Event Mapping

All treatment emergent adverse events (AEs) coded as to Body System as Nervous System Disorders using the Medical Dictionary for Regulatory Activities (MedDRA) in subjects enrolled in these studies were included in the analyses. For UCD patients, the specific toxicities reported by Thibault [35], [36], including nausea, headache, emesis, fatigue, weakness, lethargy, somnolence, dizziness, slurred speech, memory loss, confusion, and disorientation, exacerbation of neuropathy, pedal edema, hearing loss, abnormal taste, arrhythmia, rash, Kussmaul respiration, metabolic acidosis, increased anion gap, tachypnea, abdominal discomfort, cerebral edema, and obtundation or coma, were mapped to the MedDRA preferred terms in the clinical trial databases.

Analysis of AEs in Relation to PAA Levels

Analyses were based on (a) 2126 samples from 98 healthy adults, (b) 1281 blood PAA and PAGN values derived from 80 UCD patients during the short term-switchover studies who received both sodium phenylbutyrate and glycerol phenylbutyrate, and (c) 428 samples from 90 patients with cirrhosis and HE who received glycerol phenylbutyrate. Because plasma PAA levels were not always available at the time the patient was experiencing an AE, the following rules were applied to associate an AE to a known PAA level. For healthy subjects, maximum PAA values recorded after the first dose but within 24 hours of the last dose and the incidence of neurological AEs (yes/no) were summarized by dosing period; for periods where subjects received placebo or moxifloxacin, the PAA levels were set to 0. For UCD patients, maximum PAA values (Cmax) recorded during each dosing period and the incidence of neurological AEs were summarized by treatment (glycerol phenylbutyrate or sodium phenylbutyrate). For HE patients, each AE was attributed to the PAA result that was closest in time to the AE.

The contribution of a 20 μg/mL increase in PAA levels to the probability of a neurological AE regardless of relationship to the study drug was examined using Generalized Estimating Equations [39]. For healthy subjects, data were summarized for each dose group. Since UCD patients received a range of doses, data were summarized for patients receiving a dose greater or less than the median dose (equivalent to 11.7 g/day). For HE patients, neurological AEs were examined both in relation to blinded treatment group assignment; i.e. glycerol phenylbutyrate or placebo, as well as in relation to PAA levels among patients treated with glycerol phenylbutyrate.

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