Molecular Genetics and Metabolism 110 (2013) 418–423

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Minireview

Fluctuations in phenylalanine concentrations in phenylketonuria: A review of possible relationships with outcomes ☆

Maureen Cleary [a,*], Friedrich Trefz [b], Ania C. Muntau [c], François Feillet [d], Francjan J. van Spronsen [e], Alberto Burlina [f], Amaya Bélanger-Quintana [g], Maria Giżewska [h], Christoph Gasteyger [i], Esther Bettiol [i], Nenad Blau [j,k], Anita MacDonald [l]

[a] Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK
[b] School of Medicine, University of Tuebingen, Reutlingen, Germany
[c] Dr Von Hauner Children's Hospital, Ludwig-Maximilians-University, München, Germany
[d] Reference Centre for Inborn Errors of Metabolism, INSERM 954, Hôpital d'enfants Brabois, Vandoeuvre les Nancy, France
[e] Beatrix Children's Hospital, University Medical Center of Groningen, University of Groningen, Groningen, The Netherlands
[f] Division of Inherited Metabolic Diseases, Department of Paediatrics, University Hospital, Padova, Italy
[g] Hospital Ramon y Cajal, Madrid, Spain
[h] Department of Pediatrics, Endocrinology, Diabetology, Metabolic Diseases and Cardiology, Pomeranian Medical University, Szczecin, Poland
[i] Merck Serono SA Geneva, Switzerland [1]
[j] University Children's Hospital, Heidelberg, Germany
[k] University Children's Hospital, Zürich, Switzerland
[l] The Children's Hospital, Birmingham, UK

ARTICLE INFO

Article history:
Received 3 September 2013
Accepted 3 September 2013
Available online 9 September 2013

Keywords:
Phenylalanine fluctuations
Phenylketonuria
Sapropterin
Hyperphenylalaninemia

ABSTRACT

Fluctuations in blood phenylalanine concentrations may be an important determinant of intellectual outcome in patients with early and continuously treated phenylketonuria (PKU). This review evaluates the studies on phenylalanine fluctuations, factors affecting fluctuations, and if stabilizing phenylalanine concentrations affects outcomes, particularly neurocognitive outcome. Electronic literature searches of Embase and PubMed were performed for English-language publications, and the bibliographies of identified publications were also searched. In patients with PKU, phenylalanine concentrations are highest in the morning. Factors that can affect phenylalanine fluctuations include age, diet, timing and dosing of protein substitute and energy intake, dietary adherence, phenylalanine hydroxylase genotype, changes in dietary phenylalanine intake and protein metabolism, illness, and growth rate. Even distribution of phenylalanine-free protein substitute intake throughout 24 h may reduce blood phenylalanine fluctuations. Patients responsive to and treated with 6R-tetrahydrobiopterin seem to have less fluctuation in their blood phenylalanine concentrations than controls. An increase in blood phenylalanine concentration may result in increased brain and cerebrospinal fluid phenylalanine concentrations within hours. Although some evidence suggests that stabilization of blood phenylalanine concentrations may have benefits in patients with PKU, more studies are needed to distinguish the effects of blood phenylalanine fluctuations from those of poor metabolic control.

Contents

Abbreviations: BH_4, 6R-tetrahydrobiopterin; ECT, early and continuously treated; HPA, hyperphenylalaninemia; IDC, index of dietary control; IQ, intelligence quotient; LNAA, large neutral amino acid; PAH, phenylalanine hydroxylase; PKU, phenylketonuria; SD, standard deviation; SEE, standard error of the estimate; Tyr, tyrosine; WISC, Wechsler Intelligence Scale for Children.

* Corresponding author at: Department of Metabolic Medicine, Great Ormond Street Hospital for Children NHS Foundation Trust, London WC1N 3JH, UK. Fax: +44 20 7813 8258.
E-mail address: Maureen.Cleary@gosh.nhs.uk (M. Cleary).

[1] A subsidiary of Merck KGaA, Darmstadt, Germany (author's affiliation at the time of the study).

1096-7192/$ – see front matter © 2013 The Authors. Published by Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.ymgme.2013.09.001

1. Introduction

Treatment for phenylketonuria (PKU) includes diet restriction of phenylalanine intake and/or administration of 6R-tetrahydrobiopterin (BH_4) to BH_4-responsive patients. Treatment can prevent neurological impairment and mental retardation [1]. There is a consensus that, for an optimal outcome, treatment should start as early as possible and that strict blood phenylalanine level control is of primary importance, particularly during the first years of life [1]. BH_4 stimulates phenylalanine hydroxylase (PAH) activity in about 20% of patients with PKU, and in those patients it serves as a useful adjunct to the phenylalanine-restricted diet because it increases phenylalanine tolerance and allows significant dietary relaxation [2]. Sapropterin dihydrochloride (Kuvan®, Merck Serono SA Geneva, Switzerland[2] and BioMarin, Novato, CA, USA), a pharmaceutical formulation of BH_4, is an approved drug for the treatment of PKU. It has been shown to lower blood phenylalanine concentrations significantly in those patients with PKU who respond to sapropterin therapy [3–6].

A wealth of data has shown that high blood and brain phenylalanine concentrations in patients with PKU are associated with deleterious effects on neurocognitive outcomes including executive function [7,8]. Some studies have suggested that the fluctuations in phenylalanine concentrations (phenylalanine fluctuation) may be of particular significance [9–11]. Although there is currently no standard definition of *phenylalanine fluctuation*, studies reporting phenylalanine fluctuations have used the following methods for its assessment: standard deviation (SD), standard error of the estimate (SEE) of the regression of phenylalanine concentration, and mean (SD) of the index of dietary control (IDC) as measured by the mean of the 6-month median phenylalanine values [12]. Clearly, the mean of IDC requires assessment over at least 6 months, whereas SD and SEE can be assessed over shorter time frames. The mechanism by which fluctuations in phenylalanine concentrations affects outcomes is not known.

The aim of this paper is to review the literature on phenylalanine fluctuations, factors affecting fluctuations, and whether stabilizing blood and brain phenylalanine concentrations has a positive effect on outcomes, particularly on general intelligence and neurocognitive outcome.

2. Selection criteria for publications

Electronic literature searches of Embase and PubMed were performed for English-language publications on 24 May 2012 using the following terms: *phenylalanine*, *fluctuat** or *variation**, *PKU* or *phenylketonuria*, *intellectual outcome* or *IQ*, *Kuvan* or *sapropterin* or *phenoptin* or *6R-BH4* or *6RBH4* or *6R BH4* or *BH4*. The search was supplemented by additional relevant secondary references and published materials known to the authors.

The electronic literature search identified 112 papers from the search criteria used. From this search, 39 papers were identified as relevant to the subject matter of the review. Only one meta-analysis [13] and five papers reported studies assessing the impact of phenylalanine fluctuations on outcomes in patients with PKU [9–11,14,15], and one in offspring from mothers with PKU [16].

3. Fluctuations in phenylalanine concentrations

3.1. Fluctuation in healthy subjects

In healthy individuals, blood phenylalanine concentrations fluctuate by no more than 50% over 24 h [17,18]. In healthy infants and children up to the age of 18 years, reference blood phenylalanine concentrations are between 21 and 137 μmol/L, and in adults, 35 to 85 μmol/L [19–21]. Fasting blood concentrations of amino acids, including phenylalanine, are reasonably constant. Values vary throughout the day according to dietary intake, with less fluctuation with more frequent meals [17,18]. In children without PKU on a normal diet, blood phenylalanine concentrations were higher in the evening than in the morning [22].

3.2. Diurnal fluctuation in PKU

Evidence suggests that physiological fluctuations in phenylalanine concentrations in patients with PKU within a day are different to those seen in healthy individuals on a normal diet.

Inverse diurnal variation with phenylalanine concentrations that were highest in the morning was reported as early as 1969 in two children with PKU [22] and subsequently confirmed in 1985, in a pregnant 22-year-old woman with PKU [23]. Larger studies have since confirmed this inverse diurnal variation. In a study of 16 patients with classic PKU aged 1 to 18 years, the highest phenylalanine concentration occurred in the morning between 6 and 9 a.m. and the lowest between 6 p.m. and midnight in 63% of patients [24]. Diurnal variations were also demonstrated in seven patients with PKU aged less than 1 year [25]. This suggests that protein catabolism predominates over protein anabolism during fasting periods. In line with this, prolonged fasting results in a small rise in phenylalanine concentrations [26].

However, it appears that the timing of protein substitutes also affects diurnal variation. In a study of 19 patients (15 girls, 4 boys) aged 1 to 16 years, considerable fluctuation was seen between early morning and late afternoon plasma phenylalanine concentrations, which was related to intake of protein substitute [27]. In the above-mentioned study of 16 patients with classic PKU aged 1 to 18 years [24], a significant correlation was seen between the timing of protein substitute consumption and percentage change in plasma phenylalanine concentrations: the greater the quantity of protein substitute consumed by 4 p.m., the larger the decrease in daytime phenylalanine concentration ($r = -0.7030$, $p < 0.005$). The less the protein substitute consumed after 4 p.m., the larger the plasma phenylalanine concentration between 4 p.m. and 6 a.m. the following morning ($r = -0.7337$; $p < 0.005$). Similarly, in a randomized controlled study of 16 patients with well-controlled PKU, median differences in blood phenylalanine concentrations within a day were 40 μmol/L when protein substitutes were given every 4 h,

[2] A subsidiary of Merck KGaA, Darmstadt, Germany.