J Inherit Metab Dis (2008) 31:2–3
DOI 10.1007/s10545-007-9979-1

EDITORIAL

Defining tetrahydrobiopterin (BH_4)-responsiveness in PKU

Nenad Blau

BH_4-responsive hyperphenylalaninaemia (HPA) is a recently described variant of phenylalanine hydroxylase (PAH) deficiency caused by specific mutations in the *PAH* gene. Diagnosis is performed by the tetrahydrobiopterin (BH_4) loading test (20 mg/kg body weight) and the overall prevalence of BH_4-responsiveness within patients with phenylketonuria (PKU) for blood phenylalanine reduction of 20%, 30%, 40% and 50% was found to be 48%, 38%, 31% and 24%, respectively, 8 h after the administration, and 55%, 46%, 41% and 33%, respectively, 24 h after the administration. Using the standard 30% cut-off, BH_4-responsiveness was similar regardless of the two modalities in patients with mild hyperphenylalaninaemia (79–83% responders), mild PKU (49–60% responders), and classical PKU (7–10% responders). About 46% of all HPA patients were responders 24 h post loading (Fiege and Blau 2007). BH_4 (drug name Kuvan or Sapropterin) is registered in the USA (FDA) and is currently under preregistration in Europe (EMEA) (Burnett 2007).

A number of publications have documented that a 24-hour protocol with 20 mg/kg BH_4 is the most commonly used method and that multiple administrations of BH_4 and extension of the test to up to one week may detect some additional 'slow' responders. However, some authors use lower doses of BH_4 (10 mg/kg) or a combination of phenylalanine (100 mg/kg) and BH_4 (20 mg/kg), and some authors monitor blood phenylalanine levels after repeated administration of BH_4 over a period of up to two weeks. In addition, some of the loading test experiments are performed under dietary supplementation with a low-phenylalanine food. This may result in a relative high number of initially positive responders (>50%) who did not respond to a long-term treatment, as documented by a recent multicentre study (Levy et al 2007).

In this issue of the Journal (pp. 67–72), U. Langenbeck proposes another approach for the classification of BH_4-responsiveness. He calculated the half-life ($t_{1/2}$) of blood phenylalanine at different time points following BH_4 administration. Using a log-linear regression, he compared data from several published reports with the model of a single exponential decay (SED) of blood phenylalanine. The conclusion is that only during the first 15 h after BH_4 administration does the kinetic behaviour of plasma phenylalanine obey first-order kinetics and that, with a test duration of 24 h, compatibility with the SED model is only partial. Indeed, Fiege and Blau (2007) observed that 2.7% of patients in whom the loading test was performed over 24 h were defined as responders only at 8 h. Also, 8.8% of patients were responders at 24 h, but not at 8 h. In about 15% of all patients who responded to BH_4 by 20%, blood phenylalanine levels increased from 8 h to 24 h by at least 10%. Accordingly, they suggest that the BH_4 loading test should be modified to include a second administration of 10–20 mg/kg BH_4 at time 12 h and assessment of plasma phenylalanine levels at times 0, 8, 12 and 24 h after BH_4 administrations. Thus, additional investigations are necessary in order to evaluate the importance of the 12– or 15-hour blood phenylalanine values. Long-term (1–2 weeks) loading tests are more expensive and definitely not practical for the initial screening.

N. Blau (✉)
Division of Clinical Chemistry and Biochemistry,
University Children's Hospital,
Steinwiesstrasse 75, CH-8032 Zürich, Switzerland
e-mail: nenad.blau@kispi.uzh.ch

Langenbeck further suggests in his article that genotype–phenotype analysis may benefit from the $t_{1/2}$-driven diagnostic approach and that knowledge of individual $t_{1/2}$ values and age-specific protein synthesis could improve therapeutic decisions. Data from the BIOPKU database demonstrate that the genotype-predicted BH_4-responsiveness is on average higher than that obtained from the BH_4 loading test and that the patient's genotype may certainly exclude non-responsiveness and to some extent predict a potential responder (Zurflüh et al 2008). A combination of the BH_4 loading test and genotype analysis together with the phenylalanine kinetics ($t_{1/2}$) may certainly improve the definition of the BH_4-responsiveness.

On the basis of present knowledge, guidelines for the definition of BH_4-responsiveness should include the following investigations: (1) Single loading test with BH_4 (20 mg/kg) and monitoring of blood phenylalanine at 0, 8, 12 (15), and 24 h. (2) Reduction of blood phenylalanine levels of >20–30% as an indicator for a trial with BH_4 (initial doses of 10 mg/kg) over several weeks. (3) Titration of the individual BH_4 requirement (5–20 mg/kg) to maintain optimal blood phenylalanine levels. (4) Determination of the daily phenylalanine tolerance. (5) Genotyping.

References

Burnett JR (2007) Sapropterin dihydrochloride (Kuvan/Phenoptin), an orally active synthetic form of BH_4 for the treatment of phenylketonuria. *IDrugs* **10**(11): 805–813.

Fiege B, Blau N (2007) Assessment of tetrahydrobiopterin (BH_4)-responsiveness in phenylketonuria. *J Pediatr* **150**: 627–630.

Levy L, Milanowski A, Chakrapani A, et al (2007) Efficacy of sapropterin dihydrochloride (tetrahydrobiopterin, 6*R*-BH_4) for reduction of phenylalanine concentration in patients with phenylketonuria: a phase III randomized placebo-controlled study. *Lancet* **370**: 504–510.

Zurflüh MR, Zschocke J, Lindner M, et al (2008) Molecular genetics of tetrahydrobiopterin responsive phenylalanine hydroxylase deficiency. *Hum Mutat* **29**(1): 167–175