Molecular Genetics and Metabolism 96 (2009) 158–163

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

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

Minireview

Optimizing the use of sapropterin (BH_4) in the management of phenylketonuria

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ARTICLE INFO

Article history:
Received 19 December 2008
Received in revised form 9 January 2009
Accepted 9 January 2009
Available online 8 February 2009

Keywords:
Phenylketonuria
Sapropterin
Tetrahydrobiopterin
Phe
Kuvan
Hyperphenylalaninemia

ABSTRACT

Phenylketonuria (PKU) is caused by mutations in the phenylalanine hydroxylase (*PAH*) gene, leading to deficient conversion of phenylalanine (Phe) to tyrosine and accumulation of toxic levels of Phe. A Phe-restricted diet is essential to reduce blood Phe levels and prevent long-term neurological impairment and other adverse sequelae. This diet is commenced within the first few weeks of life and current recommendations favor lifelong diet therapy. The observation of clinically significant reductions in blood Phe levels in a subset of patients with PKU following oral administration of 6R-tetrahydrobiopterin dihydrochloride (BH_4), a cofactor of PAH, raises the prospect of oral pharmacotherapy for PKU. An orally active formulation of BH_4 (sapropterin dihydrochloride; Kuvan®) is now commercially available. Clinical studies suggest that treatment with sapropterin provides better Phe control and increases dietary Phe tolerance, allowing significant relaxation, or even discontinuation, of dietary Phe restriction. Firstly, patients who may respond to this treatment need to be identified. We propose an initial 48-h loading test, followed by a 1–4-week trial of sapropterin and subsequent adjustment of the sapropterin dosage and dietary Phe intake to optimize blood Phe control. Overall, sapropterin represents a major advance in the management of PKU.

Phenylalanine (Phe) is an essential amino acid which cannot be synthesized by the human body. Its net blood level is dependent on a number of processes, including dietary and caloric intake, endogenous protein turnover, catabolism, and incorporation into proteins. After its absorption by the digestive tract, Phe is converted to tyrosine, by Phe hydroxylase (PAH) and its cofactor, 6R-tetrahydrobiopterin (BH_4): this is the major metabolic pathway of dietary Phe [1,2].

Phenylketonuria (PKU), an autosomal recessive inherited disorder characterized by defective or deficient PAH, is the cause of almost all (about 98%) cases of hyperphenylalaninemia (HPA). A minority of cases arise from disorders of BH_4 synthesis or regeneration [2,3]. The *PAH* mutation knowledgebase (hPAHdb) currently describes 532 known mutations of this gene, mostly missense mutations (61% of all mutations), deletions (14%), splice variants (11%), silent mutations (6%), and nonsense mutations (5%) [4]. A systematic review identified 29 mutations that are particularly prevalent among patients with PKU in Europe [5]. Different mutations affect the activity of PAH to different extents.

If left untreated, PKU leads to the development of a variety of clinical problems including mental retardation, microcephaly, autistic behavior, eczema, and seizures [6]. The term, PKU, is reserved for the most severe forms of PAH deficiency "classic PKU" (Phe level >1200 μmol/L). Less severe forms are mild PKU (Phe level <600–1200 μmol/L) and mild HPA (Phe level <600 μmol/L). Notwithstanding our huge experience with PKU, the distinction between PKU and mild PKU is not always that clear and differing protocols for the age of screening add to the confusion in using initial untreated, screening Phe results to classify the type of PKU.

The more severe forms present with more severe neurological diseases, if untreated. The prevalence of PKU varies by country and ethnic group, ranging from approximately 1 in 4000 births in Northern Ireland or 1 in 6500 births in Turkey to 1 in 71,000 births in Finland, and the overall estimates fall within the range of 1 case per 10,000–20,000 births in Europe and the USA [7–9].

The observation that levels of Phe can be reduced significantly by administration of exogenous BH4 in a subset of patients with PKU raises the prospect of pharmacologic management of this disease

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doi:10.1016/j.ymgme.2009.01.002

[10]. A tablet formulation of BH4 (dihydrochloride) has been available for three decades. Although this formulation has been used extensively in experimental studies, it has not been evaluated in formal clinical trials and was not registered. A newer formulation of BH4 (sapropterin dihydrochloride, Kuvan®) that is more stable at room temperature is now available for the treatment of PKU in the USA and Europe [11]. This review describes the current and potential future therapeutic use of sapropterin in the management of PKU.

Dietary management of PKU

To date, the management of all patients with PKU has focused firmly on restriction of dietary Phe, accompanied by regular monitoring of circulating levels of Phe. Current recommendations on target Phe levels are 120–360 μmol/L for the first 10–12 years of life [12]. These recommendations, however, differ from country to country. Dietary Phe restriction, ideally begun within 1–2 weeks after birth, is effective in protecting the developing central nervous system from the toxic effects of HPA, although differences in cognitive function, behavior, or educational achievement have been observed between early-treated subjects with PKU and control populations [13–15]. There is an increasingly held view that dietary treatment for this condition should be lifelong [16,17]. Long-term outcome studies showed that adults with non-restricted diets may have some brain MRI disturbance or speed processing deficiencies [18–21]. The optimal Phe level in adulthood is widely debated. The behavior of some adult patients improves when they return to an appropriate diet (maternal PKU), but the burden of the regimen is still difficult to support. Treatment with BH_4 not only helps to improve Phe levels, but also eases the burden of dietary management and should thereby improve dietary compliance issues in a subset of PKU patients who are BH4-responders.

Adhering to a low-Phe diet is onerous. The diet is supplemented with Phe-free protein substitutes consisting of essential and non-essential amino acids, and it excludes many natural high-protein foods such as dairy products, meat, and fish [22–24]. Commercial Phe-free amino acid supplements, designed for use by individuals with PKU, may have an unappealing taste or smell, and the Phe-restricted diet has been associated with adverse feeding behaviors in young subjects [25,26]. Nutritional deficiencies with clinical relevance have also been observed in diet-treated patients with PKU [23,27]. Newer protein substitutes may offer better tolerability and convenience for patients, but the burden of the diet remains a major cause for the loss of compliance, as observed in patients beyond childhood with PKU [24,28,29].

Therapeutic use of tetrahydrobiopterin in the management of PKU

Rationale

Clinically significant reductions in blood Phe in response to oral administration of exogenous BH4 (using the unregistered formulation) have been observed in about 80% of patients with mild HPA, in about 50% of patients with mild PKU, and in $\leqslant$10% of patients with classical PKU. A decrease in blood Phe of at least 30% is often used as a cut-off value to determine treatment response, although this is arbitrary [30,31]. Continued administration of this 6R-BH4 preparation (up to 5 years) has been shown to maintain reductions in blood levels of Phe without adverse effects [32,33].

Therapeutic profile of sapropterin in patients with PKU

Controlled clinical trials have evaluated the efficacy of a pharmaceutical formulation of sapropterin (Kuvan®), in patients with PKU (Table 1) [34–38]. Overall, the results of these trials indicated that about 20–50% of patients with PKU achieved a reduction in blood Phe of $\geqslant$30%. A study in 489 patients (mean age: 22 years; range 8–49 years) showed that 8 days of sapropterin (10 mg/kg/day) reduced mean plasma Phe by $\geqslant$30% in about one-fifth of patients (Fig. 1A), with a mean change in blood Phe of −392 ± 185 μmol/L) [34]. An analysis of responders to treatment in this trial confirmed the efficacy of sapropterin versus placebo (Fig. 1B) [35]. Further studies showed that the effects on blood Phe are dose-related (Fig. 2) and are durable over time (Fig. 3) [35].

One study, performed in a pediatric population, recorded the amount of Phe supplementation possible while maintaining blood Phe at <360 μmol/L. These data were consistent with earlier data from a 2-year evaluation of the unregistered preparation of BH_4, in which daily Phe tolerance increased from 18 mg/kg before treatment to 40 mg/kg during treatment [33].

Sapropterin is effective in reducing plasma Phe concentrations in a dose-dependent manner and is well tolerated at doses of 5–20 mg/kg/day over 22 weeks in BH_4-responsive patients with PKU [39]. Headache, upper respiratory tract infections, and rhinorrhea were the most common side-effects observed in sapropterin-treated patients with PKU in clinical trials [35,37,38].

Optimizing sapropterin therapy

Who to test?

Sapropterin will be used for the treatment of HPA in patients with PKU who have been shown to be responsive to such treatment. Thus, all patients with PKU should undergo a sapropterin oral-response test before treatment initiation [40]. In Europe, the BH4-loading test is mostly performed in the neonatal period. In the neonatal period Phe levels are high and it is practical to perform the test. In instances where the child is under strict dietary control, a Phe 'challenge' (100 mg/kg) must precede the BH4 administration; however, there is no clear recommendation how to interpret the data without a preceding single Phe load. Also, it is contentious whether one should perform such a challenge at all. A number of different protocols have been followed using the unregistered BH4 formulation and sapropterin [31,34,41,42]. These studies have included using a normal diet or a Phe-restricted diet, different doses of BH4, different time periods to assess the effect on blood Phe (a 24-h test may detect slower responders more effectively than an 8-h test), single dose or multiple dose treatment administration, and the measurement of blood Phe levels or the half-life of decreases in blood Phe [40]. It should be noted that a $\geqslant$30% reduction in blood Phe is often considered to represent a clinically significant response to treatment; however, it is important to note that this threshold is arbitrary and some medical professionals consider smaller reductions to be clinically significant. Clearly, a simple and universal loading test would facilitate the identification of responders to sapropterin. Such a test must be practical in its application, being sufficiently predictive for BH4 responsiveness while restraining the number of measurements that need to be made.

Current protocol for treatment initiation

Fig. 4A shows the algorithm approved by the US Food and Drug Administration (FDA) for initiating therapy with sapropterin in patients above 4 years of age [37]. The prescribing Information for this product does not provide a specific cut-off value for a clinically significant reduction in blood Phe [37]. According to the FDA-approved algorithm, a measurement of blood Phe is followed by an initial daily dose of sapropterin, 10 mg/kg/day, given for 1 week, at the end of which a repeat blood Phe measurement is taken. If