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Original article

Long-term follow-up of tetrahydrobiopterin therapy in patients with tetrahydrobiopterin deficiency in Japan

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Abstract

Tetrahydrobiopterin (BH_4) deficiency is a rare, congenital and lethal condition resulting in phenylalanine build-up that can lead to mental retardation and developmental defects, unless properly treated. About 1 million newborn infants in Japan undergo neonatal PKU screening every year, of which about 1 in 2 million are diagnosed with the condition. In this post-marketing surveillance study, 19 patients with BH_4 deficiency in whom BH_4 supplementation with sapropterin dihydrochloride (Biopten®) (hereafter referred to as 'BH_4 therapy') was initiated before the age of 4 years, were followed up for ⩽28 years. Patients who screened positive for BH_4 deficiency were treated with supplemental BH_4 plus L-dopa and 5-hydroxytryptophan. Data on the patients' clinical courses were collected once yearly at 10 medical centers in Japan. Seventeen patients were diagnosed with 6-pyruvoyl tetrahydropterin synthase deficiency and two with dihydropteridine reductase deficiency at an average age of 3.6 months; the mean age at end of follow-up was 14.6 years. Average duration of BH_4 therapy (mean dose, 5 mg/kg per day) was 13.2 years. Serum phenylalanine was reduced from more than 10 mg/dL at the start of drug administration to less than 2 mg/dL at end of follow-up. No abnormalities in height or weight were observed in any patients, except for one female patient with familial obesity. No unwarranted side effects were reported throughout the long-term course of treatment, even during pregnancy. BH_4 therapy can effectively maintain serum phenylalanine levels within the normal range in patients with BH_4 deficiency, and demonstrated excellent long-term safety, with no side effects.

Keywords: Tetrahydrobiopterin deficiency; Biopten; Sapropterin; Hyperphenylalaninemia; PKU

1. Introduction

Phenylketonuria (PKU) and hyperphenylalaninemia (HPA) in infants are markers indicative of a congenital deficiency of tetrahydrobiopterin (BH_4), an essential cofactor in the enzymatic biosynthesis of nitric oxide and several neurotransmitters. High levels of phenylalanine in the brain due to untreated BH_4 deficiency are severely neurotoxic, and can lead to mental retardation and developmental defects [1,2]. About 1 million newborn infants in Japan undergo neonatal mass screening for PKU every year, since the program was started in 1977. The incidence of HPA in Japan is about 1 in 80,000, lower than in Europe [1,2]. However, BH_4 deficiency occurs in about 1 in 2 million Japanese people, in line with the global average frequency [3]. Thirty-two patients with BH_4 deficiency in Japan are currently being treated with sapropterin hydrochloride, an active form of BH_4 (R-BH_4), which was developed in Japan in 1981 (hereafter referred to as 'BH_4 therapy').

Sapropterin dihydrochloride granules 2.5%; Biopten® (Daiichi Sankyo, Japan) was approved in Japan 1992 to decrease serum phenylalanine values in HPA (atypical HPA) due to dihydrobiopterin synthase (DHBS) deficiency

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or dihydropteridine reductase (DHPR) deficiency. Since 2008, Biopten® has been further approved to decrease serum phenylalanine values in HPA due to BH_4-responsive hyperphenylalaninemia (BH_4-responsive HPA).

Postmarketing surveillance of Biopten® for BH_4 deficiency has been underway in Japan for the last 16 years. In this study, we assessed the efficacy and safety of this agent in 19 patients with BH_4 deficiency in whom treatment was initiated before the age of 4 years.

2. Patients and methods

Among 19 HPA patients detected by neonatal PKU screening in Japan (Table 1), 17 were diagnosed with 6-pyruvoyl tetrahydropterin synthase (PTPS) deficiency based on pteridine analysis of urine or serum, whereas two were diagnosed with DHPR deficiency, based on Guthrie test results. All 19 patients were diagnosed with BH_4 deficiency and received treatment with BH_4, L-dopa, and 5-hydroxytryptophan (5-HTP), initiated before the age of 4 years, between 1982 and 2008.

This study was performed as a post-marketing surveillance study at 10 medical centers in Japan, between April 1992 and December 2008. During this period, the doctors in charge reported annually on the patients' heights, weights, serum phenylalanine concentrations, BH_4 dosages, concomitant medications, and provided information on drug effectiveness and safety in accordance with regulated survey slips. Similar information was retrospectively collected from clinical records available between 1982 and 1991.

Serum phenylalanine concentrations were determined using an automated amino acid analyzer (L-8800; Hitachi, Tokyo, Japan). Serum pteridine was measured by high-performance liquid chromatography (LC-10; Shimazu, Kyoto, Japan) after iodine oxidation. DHPR activity was measured using Guthrie card specimens, as described previously [4].

Table 1
Baseline characteristics.

Parameter	*n* (%)
Type	
PTPS deficiency	17 (89.5)
DHPR deficiency	2 (10.5)
Sex (M/F)	10/9 (52.6/47.4)
Hospitalization	
Outpatients	11 (57.9)
In ↔ out	8 (42.1)
Age at initiation of drug administration (years)	
0	16 (84.2)
1	2 (10.5)
2	0 (0.0)
3	1 (5.3)
Age at end of follow-up (years)	
0	1 (5.6)
1– < 4	4 (22.2)
4– < 10	2 (11.1)
10– < 16	1 (5.6)
⩾16	10 (55.6)
BH_4 dosage at start of therapy (mg/kg/day)	
<5	8 (42.1)
5– < 10	7 (36.8)
⩾10	4 (21.1)
BH_4 dosage at end of follow-up (mg/kg/day)	
<5	7 (36.8)
5– < 10	4 (21.0)
⩾10	8 (42.1)
L-dopa use during follow-up	
Yes	19 (100.0)
No	0 (0.0)
5-HTP use during follow-up	
Yes	19 (100.0)
No	0 (0.0)
Phenylalanine-restricted diet during follow-up	
Yes	12 (63.2)
No	6 (31.6)
Unknown	1 (5.3)
Blood phenylalanine level at neonatal mass screening (mg/dL)*	
Mean	14.2
Range	6.0–48.9

* Data available for 13 patients.

3. Results

Patients' background clinical characteristics are shown in Table 1. Seventeen patients were diagnosed with PTPS deficiency and two with DHPR deficiency; the mean age at end of follow-up was 14.6 years, and the mean age at initiation of BH_4 supplementation was 3.6 months. The mean duration of BH_4 therapy was 13.2 years; more than half the patients received BH_4 continuously for more than 10 years. The longest treatment duration was 28 years ($n = 1$). The mean daily dosage was 5 mg/kg; eight patients received less than 5 mg/kg and 11 patients received more than 10 mg/kg.

Changes in BH_4 dosage with age are shown in Fig. 1. The mean dosage in patients with PTPS deficiency increased over the initial few years of treatment, then remained stable thereafter. As of 2008, the average daily dose in 15 patients with PTPS deficiency was 7.9 mg/kg (Fig. 1). Of the two patients with DHPR deficiency, one was controlled by a stable dose, while the other required a high dose to control their serum phenylalanine level (Fig. 2).

Serum phenylalanine values in 13 of the 19 cases for whom data were available at the time of newborn screening are shown in Table 1. Changes in serum phenylalanine levels in patients with PTPS deficiency are shown in Fig. 2a. Serum phenylalanine was high (10 mg/dL) at the start of drug administration, but decreased to less than 2 mg/dL following Biopten® administration, with good phenylalaninemic control being maintained thereafter (Fig. 2a).

However, one patient with deficiency of DHPR, an enzyme responsible for BH_4 recycling, struggled to con-