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종 설

Role of Tetrahydrobiopterin (BH_4) Therapy in PKU

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Tetrahydrobiopterin (BH_4) can normalize blood phenylalanine (Phe) levels in BH4 deficiency, but typically not in phenylketonuria (PKU). In 1999, Kure et al. reported that some PKU patients showed decreased blood Phe levels after BH_4 loading, and thereafter, those PKU patients were identified by neonatal PKU screening. A natural cofactor for phenylalanine hydroxylase (PAH) is a 6R-isomer of BH_4, which is first synthesized in Japan as Sapropterin dihydrochloride (Biopten®) in 1982. In Japan, Biopten® is first approved for the treatment of BH_4 deficiency in 1992, and then for BH_4-responsive PAH deficiency (BPKU) in 2008. The discovery of BPKU has vast clinical implications. After Biopten® (Kuvan®) is available for the treatment of BPKU, the QOL of both patients and their families were improved very much, since the serum phenylalanine levels were controlled within 4 mg/dL by BH_4 mono-therapy with a normal diet or BH_4 combined use of mild phenylalanine-restricted diet. Biopten® therapy in patients with BPKU is highly efficacious (70%) at maintaining serum Phe levels within recommended control range and provides excellent safety at least average use period of 10 years (range, 1-17 years) with no unwarranted side effects in Japan. In addition it has been confirmed that sapropterin therapy initiated before 4 years of age was very effective to maintain plasma Phe levels within the favorable range and was safe in Japanese patients with BPKU.

Key words: PKU, Tetrahydrobiopterin, BH4 responsive hyperphenylalaninemia, Diet therapy

Introduction

The role of tetrahydrobiopterin (BH_4) treatment began to BH_4 deficiency. It was developed into the treatment of PKU. Sapropterin dihydrochloride, a tetrahydrobiopterin (BH_4) drug, was approved for the treatment of patients with BH_4-responsive phenylalanine hydroxylase (PAH) deficiency based on clinical trial data in patients over 4 years of age in the United States. Yet, many patients under 4 years have been treated with sapropterin since its approval. In Japan, sapropterin dihydrochloride granules 2.5% (Biopten®, Daiichi Sankyo, Japan) was approved in 1992 for treatment of BH_4 deficiency and in 2008 for treatment of BH_4-responsive PAH deficiency (BPKU). Efficacy and safety of BH_4 therapy in PKU will be described here.

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[A novel therapeutic strategy for phenylketonuria (PKU) has been initiated in Japan][1-3]

In 1999, Kure et al.[1] reported four patients with PAH deficiency who showed a decrease in blood phenylalanine elevations after BH_4 loading. BH_4 is known to normalize blood phenylalanine in

BH_4 deficiency, but not in PKU. However, we also found that 5 patients of 15 with mild HPA (serum phenylalanine <20 mg/dL) showed a gradual decrease of serum phenylalanine at 24 hr with BH_4 loading, although no patient with classical PKU (serum phenylalanine ≧20 mg/dL) responded to BH_4[2].

In 2004 we reported long-term treatment and diagnosis of BH_4-responsive HPA with a mutant PAH gene[3]. The criterion standard was administered to a total of 12 patients with BPKU with a mutant PAH gene at 12 medical centers in Japan between June 1995 and July 2001. The therapeutic efficacy of BH_4 was evaluated in single-dose, four-dose, and 1-week BH_4 loading tests followed by long-term-BH_4 treatment, and was also examined in relation to the PAH gene mutations. The endpoints determined were the percent decline in serum phenylalanine from initial values after single-dose (>20%), four-dose (>30%), and 1-week BH_4 (>50%) loading tests. Patients with mild PKU exhibiting decreases in blood phenylalanine concentrations of greater than 20% in the single-dose test also demonstrated decreases of greater than 30% in the four-dose test (Fig. 1). The 1-week test elicited BH_4 responsiveness even in patients with poor responses in the shorter tests. Patients with mild HPA, many of whom carry the R241C allele, responded to BH_4 administration. No clear correlation was noted between the degree of decrease in serum phenylalanine concentrations in the single- or four-dose tests

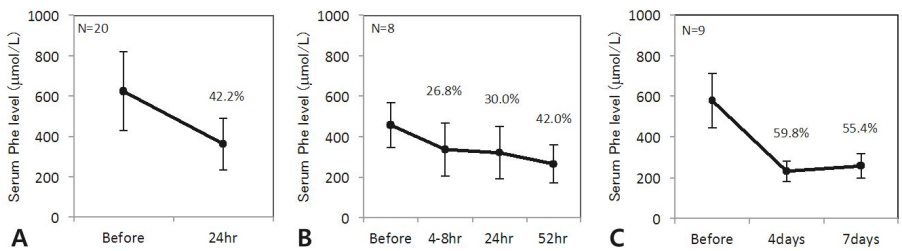

Fig. 1. BH_4 loading test.

Table 1. Maximum Lowering Rate (%) in Single-, 4-time- and 1-week-BH_4-loading Tests, and PKU Genotype in 12 Patients

Patients No.	Maximum lowering rate (%) in loading test			PKU genotype	
	Single-BH_4 (10 mg/kg)	4-time-BH_4 (15 mg/kg)	1-week-BH_4 (20 mg/kg)	Allele 1	Allele 2
Case 1	33.7	55.8	44.7	R241C	T278I
Case 2	53.5	62.4	80.0	P407S	R158W
Case 3	51.4	35.1	60.1	A132V	R413P
Case 4	0.4	37.4	50.2	R241C	R241C
Case 5	20.6	15.6	75.2	R241C	P281A
Case 6	58.9	45.9		P407S	R252W
Case 7	43.1	-	-	R241C	R413P
Case 8	39.0	59.4	70.8	R241C	R111X
Case 9	58.6	58.6	-	A373T	IVS4-1g>a
Case 10	41.7	41.7	48.1	R241C	R413P
Case 11	61.7	61.7	-	R241C	R241C
Case 12	-	-	56.3	R241C	R413P

and specific PAH mutations (Table 1). The 1-week test (20 mg/kg of BH_4 per day) is the most sensitive test for the diagnosis of BPKU. Responsiveness apparently depends on mutations in the PAH gene that cause mild PKU, such as R241C. BH_4 proved to be an effective therapy that may be able to replace or liberalize the phenylalanine-restricted diets for a considerable number of patients with mild PKU.

[Long-term follow-up of BH4 therapy in patients with BH4 deficiency in Japan][4)]

In 2013 we reported the safety and efficacy of long-term (16 years) treatment with sapropterin in BH_4-deficient patients whose treatment started before the age of 4 years based on postmarketing surveillance in Japan[4)]. Data on the patients' clinical courses were collected once yearly at 10 medical centers in Japan. Seventeen patients were diagnosed with6-pyruvoyl tetrahydropterin synthase (PTPS) deficiency and two with dihydropteridine reductase (DHPR) 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 treatment (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. Bioptен® therapy can effectively maintain serum phenylalanine levels within the normal range in patients with BH_4 deficiency (Fig. 2), and demonstrated excellent long-term safety, with no side effects.

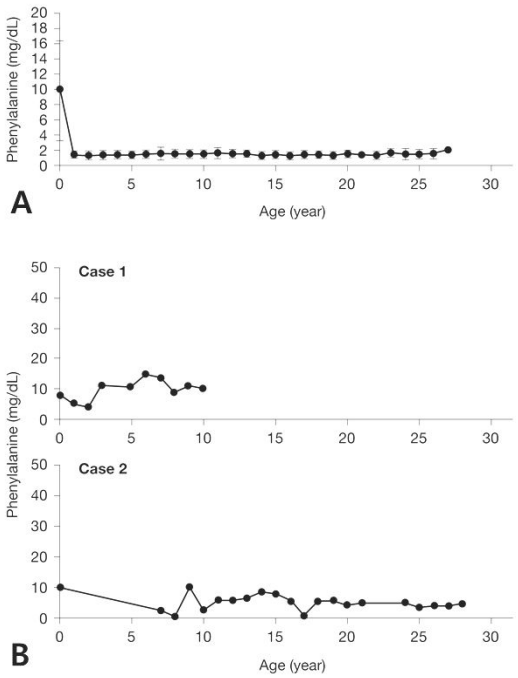

Fig. 2. Changes in serum phenylalanine levels in patients with (A) PTPS deficiency (n=17) and (B) DHPR deficiency (cases 1 and 2).

[Long-term follow-up of BH_4 therapy in patients with BPKU in Japan][5)]

In 2014, we report the long-term safety and efficacy of sapropterin in patients with BPKU whose treatment was initiated before the age of 4 years. We analyzed a longitudinal follow-up study conducted in all patients with BPKU throughout Japan. At the end of 2011, 43 patients were receiving sapropterin, of whom 21 were aged <4 years at the initiation of treatment. The starting dose of sapropterin was ≥10 mg/kg/day in 11 of these 21 patients. The duration of follow-up was ≥4 years in 6 of those 11 patients; 3 of these 6 were followed for ≥10 years. Nine patients were receiving sapropterin monotherapy at the end of 2011. Serum phenylalanine level was maintained

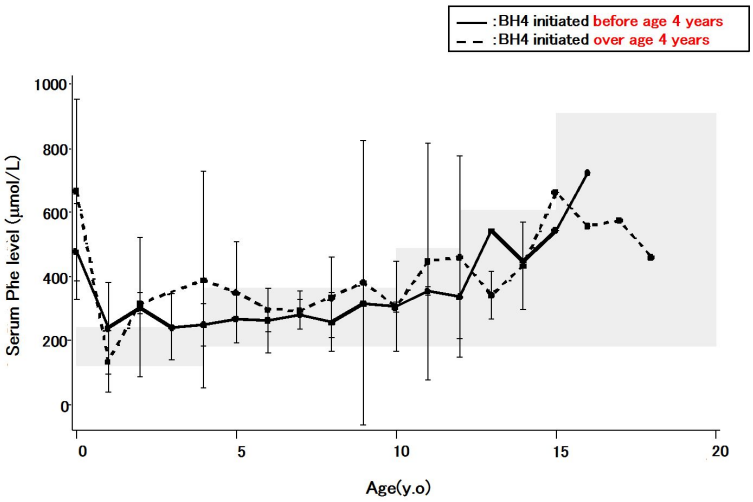

Fig. 3. Serum phenylalanine levels in patients with BPKU whose treatment was initiated before and after the age of 4 years.

within the recommended optimal control range in all 21 patients who started sapropterin treatment before age 4 years (Fig. 3). Only 1 nonserious adverse drug reaction occurred, an elevated alanine aminotransferase (ALT) level in 1 patient. No significant abnormal behavior related to nerve disorders was reported.

Sapropterin therapy initiated before age 4 years was effective in maintaining serum phenylalanine level within the favorable range and was safe in Japanese patients with BPKU.

Conclusions

Sapropterin therapy is effective in controlling plasma Phe levels within the normal range in patients with BPKU, with excellent long-term safety and no unwarranted side effects. Twenty-one patients with BPKU in Japan treated with sapropterin initiated before the age of 4 years have been followed for up to 16 years, providing a unique long-term follow-up in this population. BPKU requires lifelong drug treatment, and a high degree of drug safety is therefore required. The results of our long-term study suggest that sapropterin is associated with a high degree of safety, even when treatment is initiated at ages younger than studied in clinical trials.

References

1) Kure S, Hou DC, Ohura T, Iwamoto H, Suzuki S, Sugiyama N, et al. Tetrahydrobiopterin-responsive phenylalanine hydroxylase deficiency. J Pediatr 1999;135:375-8.
2) Shintaku H, Asada M, Sawada Y, Yamano T. Tetrahydrobiopterin-responsive hyperphenylalaninemia without biopterin deficiency. Pteridines 2000;11:83-4.
3) Shintaku H, Kure S, Ohura T, Okano Y, Ohwada M, Sugiyama N, et al. Long-term treatment and diagnosis of tetrahydrobiopterin-responsive hyperphenylalaninemia with a mutant phenylalanine hydroxylase gene. Pediatr Res 2004;55:425-30.
4) Shintaku H, Ohwada M. Long-term follow-up of tetrahydrobiopterin therapy in patients with tetrahydrobiopterin deficiency in Japan. Brain Dev 2013;35:406-10.
5) Shintaku H, Ohura T. Sapropterin is safe and effective in patients less than 4-years-old with BH4-responsive phenylalanine hydrolase deficiency. J Pediatr 2014;165:1241-4.