Tetrahydrobiopterin Therapy for Phenylketonuria in Infants and Young Children

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Objective To describe patient selection, treatment administration, response evaluation, and side effect management associated with sapropterin therapy in infants and children aged <4 years.

Study design Six case reports are presented from 4 US metabolic clinics treating phenylketonuria with sapropterin in patients aged 7 months to 4 years. Outcomes included blood phenylalanine (Phe) levels before and during treatment. For 3 of 6 cases, diet records were used to monitor changes in dietary Phe.

Results Severity of phenylketonuria ranged from mild to severe (classic). Treatment with sapropterin was safe and generally well tolerated. Blood Phe levels were reduced, or maximum dietary Phe tolerance was increased in patients with blood Phe that was well controlled by diet.

Conclusions Given the increasing evidence that maintaining blood Phe levels below 360 μmol/L is important for the normal development of neurocognitive and behavioral function, sapropterin can be combined with a Phe-restricted diet to control blood Phe levels in young patients responsive to sapropterin therapy. *(J Pediatr 2011;158:410-5)*.

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Phenylketonuria (PKU) is an inherited metabolic disorder involving a group of genetic mutations that reduce the ability of the enzyme phenylalanine hydroxylase (PAH) to convert phenylalanine (Phe) to tyrosine, leading to an accumulation of Phe in the blood and brain. Dietary therapy for this disorder has virtually eliminated the incidence of severe mental deficits and other physical ailments (eg, seizures, skin problems, microcephaly) caused by high Phe levels during infancy. However, the Phe-restricted diet has limitations related to cost, palatability, nutritional adequacy, and convenience, which often lead to reduced adherence to the prescribed diet during adolescence. In the past, it was common practice to recommend eliminating the Phe-restricted diet in school-aged children, when brain development was presumed to be complete. Accumulating evidence on behavior and cognitive development suggests that patients who remain on the diet do better than patients who discontinue the diet,[1-5] and it is now standard practice for clinics to recommend a Phe-restricted "diet for life." [6]

In December 2007, the US Food and Drug Administration approved sapropterin dihydrochloride (sapropterin), a synthetic version of the naturally occurring PAH cofactor tetrahydrobiopterin (BH_4), for the treatment of PKU. In BH_4-responsive patients, sapropterin can be combined with a Phe-restricted diet to further reduce elevated blood Phe levels. Although there are no age restrictions associated with the use of sapropterin in the United States,[7] clinical trials that contributed to the Food and Drug Administration approval included only subjects aged 4 years and older.[8-10] Given the lack of data for this age group, some clinicians have been hesitant to prescribe treatment for patients aged <4 years. Furthermore, sapropterin has been approved for use in the European Union with an age restriction excluding this age group.[11] In the 18 months since sapropterin was approved for use in the United States, a number of clinics have begun treating infants and young children aged <4 years. The objectives of this report are to share the experiences of some of these clinics with regard to patient selection, treatment administration, response evaluation, and side effect management, and to discuss treatment issues associated with this patient population.

Methods

The methods described herein are applicable to the patient cases presented in the Results section. Case-specific modifications of or additions to these methods are

BH_4	Tetrahydrobiopterin
OFC	Occipital-frontal circumference
PAH	Phenylalanine hydroxylase
Phe	Phenylalanine
PKU	Phenylketonuria

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noted in the individual case presentations. Because no clinic has extensive experience with sapropterin treatment in the 0- to 4-year age group, it did not seem appropriate to provide summary statistics based on the small sample sizes for each clinic. Instead, contributing clinics were asked to provide one or two cases that demonstrated an interesting aspect of treatment.

Patients selected for treatment were diagnosed through newborn screening and screened for primary BH_4 deficiency. Five out of the 6 patients were started on a Phe-restricted diet by 15 days of life. The blood Phe level for the sixth patient was not sufficiently elevated to warrant treatment after identification by newborn screening, so that patient was never started on the diet. Treatment with sapropterin was initiated between age 7 months and 4 years in patients with baseline blood Phe levels ranging from 72 to 810 μmol/L.

In general, testing for responsiveness to sapropterin involved determining blood Phe levels just before initiating treatment. Dosing was weight-based, starting at either 10 or 20 mg/kg/day, and tablets were administered by crushing and/or dissolving in water, apple juice, or formula. Parents were advised not to change their child's diet during the period of testing for responsiveness. For 3 of the 6 patients, diet records were available to determine the amount of Phe consumed before and during treatment. Blood Phe levels were tested again at regular intervals (which differed from case to case). Responsiveness to sapropterin was defined as either a clinically significant decline in blood Phe level or a demonstrated increase in dietary Phe tolerance while blood Phe level was maintained within the desired range.

Results

Case 1

This girl was diagnosed with classic PKU based on a blood Phe level of 2460 μmol/L and was started on a diet of Phe-free medical formula at approximately 1 month of age. For the first 3 years of life, the patient and her family were compliant with the Phe-restricted diet, providing daily diet records and blood Phe samples on a regular basis. Blood Phe level remained in excellent control, varying from 30 to 384 μmol/L (excluding periods of illness), with an average of 192 $\pm$ 90 μmol/L. A total of 78 measurements were recorded. During this period, the patient developed normally, following the appropriate percentiles for growth in weight, height, and occipital-frontal circumference (OFC).

At age 3 years, 1 month, the patient was tested for responsiveness to sapropterin. When testing was initiated, the patient's diet consisted of 90 g of Phe-free formula and 330 mg of Phe from 6.6 g of natural protein. Her weight was 17 kg. She was started on a sapropterin dose of 300 mg, or 17.6 mg/kg/day. This dose was increased to 400 mg, or 21.4 mg/kg/day, when she reached 18.7 kg in July 2008. The patient's average blood Phe for the 6 levels recorded before the start of treatment was 227 $\pm$ 107 μmol/L, which was similar to the average for the previous 3 years (192 μmol/L). As shown in Figure 1, her blood Phe level just before starting treatment (72 μmol/L) was well below this level. For the first 5 weeks of testing, her blood Phe level averaged 104 $\pm$ 46 μmol/L, representing a decrease of 54% compared with the mean value before the start of therapy. At this point, dietary Phe tolerance was tested by increasing Phe intake. As Phe intake increased from 330 to 1100 mg/day, blood Phe level increased from 60 to a maximum of 550 μmol/L. Dietary Phe intake was then decreased and maintained at approximately 900 mg/day. During this period, the average blood Phe level was 192 $\pm$ 65 μmol/L, representing a 15% decrease relative to pretreatment levels. For this patient, blood Phe level did not decrease substantially relative to baseline, but the patient's dietary Phe intake almost tripled, allowing for a significant increase of natural protein in the diet.

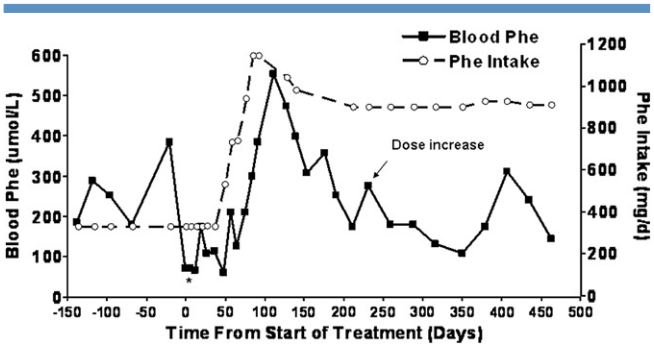

Figure 1. Blood Phe levels (left axis) and Phe intake (right axis) for Case 1. Day 0 represents the start of sapropterin treatment. The *arrow* indicates time at which the sapropterin dose was increased.

After maximum Phe tolerance was determined, the patient's Phe intake from foods was slowly increased and Phe from nonfat dry milk was decreased until all 900 mg of Phe was coming from natural protein sources. The patient has slowly added higher-Phe grain products and some yogurt to her diet while decreasing the amount of low-protein foods. There were no reports of adverse events or problems with dosing or administration during treatment, and she has continued to grow and develop normally.

Case 2

This girl was diagnosed with classic PKU at 7 days after birth, with a blood Phe level of 1902 μmol/L, at which time she was placed on a Phe-restricted diet of breast milk and Phe-free formula. In the 10 months before starting sapropterin treatment, the patient and family were relatively compliant with the PKU diet and provided blood Phe samples on a regular basis (41 samples). The patient's average blood Phe level was 217 $\pm$ 111 μmol/L (range, 36-426 μmol/L). Her dietary Phe intake during this 10-month period ranged from 182 to 289 mg/day (22-63 mg/kg/day). Her development during this period was normal, with consistent growth percentiles for weight, height, and OFC.