



Use of Tetrahydrobiopterin (Sapropterin) During Pregnancy

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Abstract

A reported 30-50% of patients with phenylketonuria (PKU) receiving treatment with tetrahydrobiopterin (BH⁴) respond with a reduction in plasma phenylalanine (Phe) levels. Sapropterin, a formulation of BH⁴, is USFDA approved as Kuvan[®] for treatment of PKU as an adjunct to traditional dietary therapy. Treatment of PKU with Kuvan[®] during pregnancy has not been systematically studied, and few cases have been previously reported. In the FDA use in pregnancy ratings, Kuvan[®] is classified as Class C because pregnant animal studies have not been conducted and there are no well-controlled studies in pregnant women.

We report the case of JB, a 29-year-old PKU patient treated with Kuvan[®] during pregnancy. Prior to conception, she demonstrated responsiveness and received pre-pregnancy counseling regarding comparative risks of PKU embryopathy and any unknown effects of Kuvan[®] use in pregnancy. Mean plasma Phe on diet restriction alone prior to administration of Kuvan[®] was 8.7 mg/dl; higher than the recommended treatment range of 2-4 mg/dl for pregnancy. After starting Kuvan[®], and prior to conception, plasma Phe dropped to a mean of 3.6 mg/dl with only moderate dietary Phe restriction. JB maintained a mean plasma Phe of 2.7 mg/dl throughout pregnancy, and continued to tolerate the drug well. She experienced anorexia and nausea of the first trimester, accompanied by decreased caloric intake. Despite endogenous protein catabolism, plasma Phe levels remained stable within treatment range in the first trimester. In the second and third trimesters, continual increase of dietary protein was required to maintain appropriate Phe levels. Targeted ultrasounds during pregnancy revealed no fetal anomalies or growth abnormalities, and the newborn (GB) exhibited normal neurologic and physical development with no dysmorphic findings on detailed clinical evaluation. GB continues to develop normally. Although limited information is available, Kuvan[®] in pregnancy appears to be well-tolerated without adverse effects to the fetus.

Introduction

PKU is an inherited deficiency of the enzyme phenylalanine hydroxylase (PAH), causing elevated plasma Phe and deficient plasma tyrosine (Tyr). Traditional PKU treatment is a combination of dietary Phe restriction and supplementation of deficient nutrients with a metabolic formula. During pregnancy, high maternal plasma Phe is actively transported to the developing fetus and can cause PKU embryopathy: microcephaly, mental retardation, intrauterine growth restriction, congenital heart disease, and other birth defects. Fetal risk increases proportionally with increased maternal Phe levels. Maternal plasma Phe ≥ 10 mg/dl correlates with more severe abnormalities and greater decrease in childhood IQ.¹ Many women who discontinue or relax dietary therapy prior to pregnancy have difficulty achieving the strict blood Phe control known to limit PKU embryopathy risk. BH⁴, a PAH cofactor, has been studied for use in PKU treatment. Clinical trials of sapropterin show 30-50% of PKU patients trialed respond with decreased plasma Phe levels.² Kuvan[®] (BioMarin Pharmaceutical, Inc.) is FDA approved for safety and efficacy in PKU treatment, but is designated Class C for use in pregnancy because "there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks".³ Case studies with good outcomes of sapropterin use in pregnancy have been reported.³

History

JB, a 29 year old female with PKU, presented to genetics clinic for pre-pregnancy diet counseling. By report, newborn plasma Phe was 15 mg/dl, and childhood levels ranged from 2-10 mg/dl with minimal diet restriction and no metabolic formula. She completed college and has normal cognition. Plasma Phe of 10.2 mg/dl, and Tyr of 1.2 mg/dl was measured, on an unrestricted diet. Dietary intervention achieved a mean plasma Phe of 8.7 mg/dl. Adherence to dietary therapy sufficient to decrease plasma Phe to levels safe for pregnancy was complicated by a history of minimal dietary restriction and intolerance of metabolic formula.

Methods and Intervention

Sapropterin treatment was initiated through an Expanded Access Program prior to FDA approval of Kuvan[®]. Dosing at 20 mg/kg was based on adjusted body weight (ABW) of 80.2 kg due to obesity. Dose per total body weight was 14.3 mg/kg. JB received 1600 mg/day (16 tablets). Lifestyle and a moderate dietary Phe restriction remained unchanged. Baseline plasma Phe was 8.5 mg/dl. After 1 week of therapy, a response of 54% reduction in plasma Phe to 3.9 mg/dl was noted. Over 8 treatment weeks, an average 41% reduction in plasma Phe was maintained, with a mean plasma Phe of 3.6 mg/dl and a range of 2.2 - 6.2 mg/dl. Mean plasma Tyr was 0.9 mg/dl. Gastric distress, the only adverse event reported, was resolved with antacid medication and dividing Kuvan[®] tablets into am and pm doses. JB reported increased clarity of thinking with less mood volatility and lethargy. She continued Kuvan[®] by prescription with no changes in dosage or diet. **Counseling:** JB and her spouse received pre-pregnancy counseling comparing risks of PKU embryopathy and unknown effects of Kuvan[®] use in pregnancy. She chose to continue therapy and discontinue contraception.

Results

JB presented again at 7 weeks gestation. During the first trimester she reported anorexia and nausea, resulting in a decreased caloric intake. Medications included antiemetics for nausea, antacids for heartburn, and prenatal vitamins (with 1 mg folic acid). Kuvan[®] dosage, based on pre-pregnancy ABW, remained unchanged. Dietary protein was gradually increased from 50g/day (DRI for IBW=52g/d) to 80g/day (DRI for pregnancy=71g/d) to maintain adequate intake. Metabolic formula was never tolerated. Plasma Phe ranged from 2.1-3.8 mg/dl, with a mean of 3.1 mg/dl (Figure 1). Plasma Tyr ranged from 0.6-1.3 mg/dl with a mean of 0.9 mg/dl. Plasma amino acid profiles showed normal levels of essential amino acids. A healthy, normally developed female baby (GB) was delivered (Table 1). Cord blood and breast milk samples will be analyzed for sapropterin levels.

Figure 1.

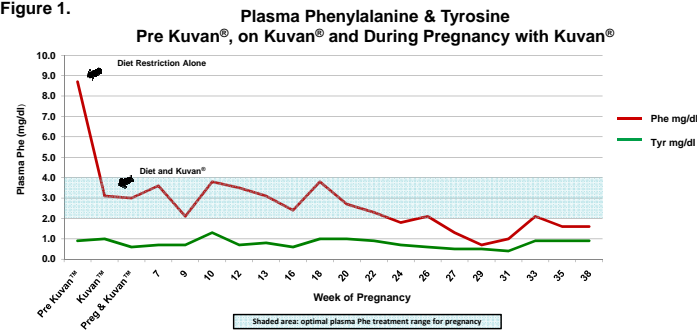


Table 1.

Pregnancy, Delivery, Infancy

JB	
Maternal BMI	40.4
Prepregnancy weight	80.2 Kg
Maternal weight gain	8.64 Kg (19 lb)
Fetal ultrasound	Normal growth, no anomalies
Diet	Moderate protein restriction liberalized during pregnancy (50g/day-80g/day)
Kuvan [®] dosing	20 mg/Kg ABW (1600 mg/day)
Medication side effects	Morning nausea (pregnancy related) Dosing split to twice a day
Pregnancy complications	Cesarean section for failure to progress
GB	
Gestational age at birth	38 weeks
Birthweight	2.838 Kg (35 th %tile)
Birth head circumference	33 cm (35 th %tile)
Birth length	49 cm (45 th %tile)
Physical Exam -- birth	APGAR 8, 9; no malformations; no dysmorphism
Physical Exam -- 3 months	Wgt 4.9 Kg (75 th %tile), HC 40.5 cm (50-75 th %tile), length 57.9 cm (10-25 th %tile)
Physical Exam -- 7 months	Wgt 7.5 kg (50 th %tile), HC 43.0 cm (50 th %tile), length 66.5 cm (25-50 th %tile)
Development -- 7 months	Babbling, sitting, crawling, pulling to stand, drinking from cup

Discussion

Women with PKU who are unable to achieve blood Phe control during pregnancy risk irreversible fetal damage of PKU embryopathy. Dietary therapy to control blood Phe levels prior to conception is preventative, but brings significant barriers to success. In the Maternal PKU Collaborative Study, 96% of mothers were off dietary therapy for 6-24 years. Only 35% reinstated diet before planning a pregnancy, and over 60% required 2-20 weeks of pregnancy to achieve control, or did not achieve it. Thus, 66% of fetuses were exposed to teratogenic blood Phe levels, causing risk for fetal anomalies during 1st trimester organogenesis and abnormal brain growth throughout pregnancy.⁴ BH⁴, formulated as sapropterin (Kuvan[®]), has been shown to reduce plasma Phe in PKU patients who respond. Kuvan[®] has received FDA approval for safety and efficacy, with Class C designation for use in pregnancy due to inadequate studies. Women with PKU, who have discontinued or relaxed dietary therapy, are often not able to achieve control of blood Phe levels in a range safe for pregnancy. Because Kuvan[®] enables some women to reduce dependence on dietary therapy for blood Phe control, it may be beneficial in preventing devastating PKU embryopathy when given during pregnancy. More study is essential.

In our patient with PKU:

1. Response to Kuvan[®] resulted in plasma Phe levels within treatment range recommended for pregnancy.
2. Kuvan[®] was well tolerated during pregnancy, without significant side effects.
3. There appear to be no harmful effects for the fetus from Kuvan[®] treatment during pregnancy; although developmental follow up is important to confirm this finding.
4. Kuvan[®] reduced dependence on dietary therapy to minimize the risk of PKU embryopathy.

References

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