



Phenylketonuria (PKU)



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Introduction

Phenylketonuria (PKU) is an inherited rare metabolic disorder (and orphan disease) caused by insufficient quantities or reduced activity of the enzyme phenylalanine hydroxylase (PAH), leading to pathologically high levels of phenylalanine (PHE) in the plasma and brain, resulting in central nervous system neurotoxicity. It is estimated that 13,000 people in the US and 50,000 people worldwide are living with PKU¹, with an overall worldwide incidence of 1:10,000 live births.² PKU is an autosomal recessive genetic disorder, meaning the child must inherit a defective gene for the disease from each parent in order to be affected by the disease. People who inherit a defective gene for the disease from one parent, and a normal gene for the trait from the other parent are carriers of the disease, but do not have the disease.

PHE is an essential amino acid that the body cannot make and must be obtained from dietary intake. The conversion of PHE to tyrosine requires a system that includes the PAH enzyme, the cofactor tetrahydrobiopterin (BH₄), and enzymes that regenerate BH₄. In patients with PKU, there is a deficiency of PAH enzyme activity that results in elevated levels of PHE. Sustained elevated blood PHE levels are toxic to the central nervous system and cause serious neurological damage including microcephaly, mood

disorders including depression, anxiety and behavioral disorders, cognitive deficiencies and mental disabilities that may be severe, seizures and tremors.³⁻⁵ Hyperactivity, hypopigmentation, and eczema may also be present in a PKU patient.

Fortunately, PKU is one of the few genetic diseases in which neurological damage and its sequelae can be prevented when diagnosis and treatment are established early. For this reason, newborn screening for PKU disease is required by law throughout the USA and other developed countries so that treatment with a low-phenylalanine diet can begin within the first few days of life. The newborn screening test is done before the baby leaves the hospital. If the initial screening test is positive, further blood and urine tests are required to confirm the diagnosis.

Complications of PKU

The most concerning complications of PKU disease are neurological and neuropsychological effects of high PHE levels. Complications secondary to PKU treatment with a highly restricted low phenylalanine diet can also occur. Long-term treatment with the low phenylalanine diet increases the risk for nutritional deficits such as vitamin and mineral deficiencies. The low phenylalanine diet should be managed closely by a dietitian specializing in PKU disease and patients' nutritional status should be monitored regularly for low levels of iron, vitamin A, zinc, and essential fatty acids. Adults with PKU are at increased risk for low bone mass and osteoporosis, despite having enough calcium and other minerals.⁵

Relationship of PKU to Cognition and IQ

The low phenylalanine diet can be very challenging to maintain, and many PKU patients experience fluctuations of plasma PHE that are well outside of the goal range for PKU disease. Transient elevations in plasma PHE are associated with neuropsychiatric problems including mood swings, anxiety, difficulty concentrating and focusing thoughts, and memory difficulties. In a study that investigated the relationship between school performance, cognitive functions, and dietary control in a group of 26 early and continuously treated PKU patients, PKU patients displayed a lower intelligence score compared to normal controls.⁶ In addition, the PKU group had a higher percentage of patients with attention problems, fine motor, and executive dysfunctions, and school problems than was seen for the group of control subjects. The index of dietary control for the last 6 months yielded a close relationship with school performance. In a separate systematic literature review and meta analysis, results confirm that there is a significant correlation between blood PHE level and IQ in patients with PKU. This research showed that for every 1.6 mg/dL increase in blood PHE level, there is a 1.3-3.1 point reduction in IQ in children from birth to 12 years and a 1.9-4.1 point average lifetime reduction in IQ.⁷



Management

The normal plasma PHE level is less than 2 mg/dL. Most PKU patients are unable to achieve plasma PHE levels in the normal range, even with close adherence to a low PHE diet. The goal of treatment for PKU is to reduce the blood PHE concentration sufficiently to prevent neurological damage, and current consensus is that patients with PKU disease should maintain a PHE level below 6 mg/dL (360 mmol/L) throughout life. The main treatment for PKU consists of reducing the amount of PHE in the diet by dietary protein restriction. Because of the severe PHE restriction required for most patients, nutritional management goals, which include support for optimal growth, development and mental function, must be closely monitored.⁸

PKU is one of the few enzyme disorders that can be managed by diet, although it requires specialized medical foods and severely restricting or eliminating foods high in PHE. Foods restricted in low PHE diets include animal protein (e.g., fish, red meat, poultry), cheese and other dairy products, legumes, and nuts.⁸ Other food types that should be limited in patients with PKU include wheat products, such as pasta and bread, certain vegetables and fruits, such as oranges and cherries. The sweetener aspartame must also be avoided, as aspartame has a high phenylalanine content. Table 1 lists the PHE content of some common foods.

Table 1. PHE contents of some typical foods

Food	Approximate PHE content (mg)
Banana (100 grams)	50
Broccoli (30 grams)	50
Rice (45 grams)	50
Baked Potato (90g)	100
Milk (90 mL)	150
Ham (100 grams)	500
One egg	700
Bread (1 slice)	300



Monitoring

Management of PKU disease is usually accomplished by the combined efforts of a physician who is a clinical geneticist and a metabolic dietician specializing in PKU disease. Patients with PKU disease often benefit from regular evaluations by a neuropsychologist specializing in PKU disease.

A safe amount of PHE differs for each person and treatment must be individualized.⁹ Maintaining a food diary, measuring and counting every mg of PHE protein in the diet, and performing regular blood tests to measure blood PHE levels is essential. Frequency of blood level monitoring is once every week during the first year, twice monthly for children 1-12 years of age, and monthly for children >12 years and adults. Normal growth, weight, evaluation of IQ, and vitamin and mineral status should also be monitored.⁸

Duration of Therapy

Neurological changes have been demonstrated within one month of birth and thus it is recommended that dietary restriction should be started as soon as possible in the newborn and continued through childhood. Until a few years ago, it was thought that patients could stop adhering to a strict PKU diet in adolescence and adulthood, after the critical time of brain development had passed. However, more recent data of brain imaging in adults with PKU has led to a consensus opinion that the PKU diet should be followed for life.⁴ In a February 2011 publication, investigators from The Netherlands and Belgium studied the effects of short-term elevation of PHE levels on neuropsychological functions and mood of adults with PKU in a randomized double-blind placebo-controlled trial.¹ They found that high plasma PHE levels have a direct negative

effect on both sustained attention and on mood in adult patients with PKU, and concluded that a PHE-restricted “diet for life” might be an advisable option for many.¹

Drug Therapy

Kuvan® (sapropterin dihydrochloride) is currently the only prescription medication FDA approved for treatment of PKU disease. Kuvan is an orally active synthetic form of tetrahydrobiopterin (BH₄). In clinical trials, Kuvan was effective in lowering PHE levels more than 30% in up to 56% of patients when used with a low PHE diet.¹⁰ But not all patients benefit from Kuvan therapy. Specifically, Kuvan therapy reduces blood PHE levels in patients with PKU disease that is responsive to BH₄.¹¹ More than 530 different disease causing PAH mutations have been identified in patients with PKU. The effect of PAH mutations on the clinical phenotype of each patient’s PKU disease is variable.⁴ Every patient is different in their PHE tolerance and PKU profile, and, in like manner, not all patients with PKU will respond to Kuvan by experiencing a clinically significant reduction in plasma PHE levels.

Currently, there is no way to predict who will respond to Kuvan. Because not all patients with PKU disease will benefit from Kuvan therapy, it is important to correctly identify those patients who will respond to Kuvan, as well as those who will not respond. Kuvan is a costly treatment, which makes accurate and timely identification of responders and non-responders of utmost importance. For most PKU patients, Kuvan will not sufficiently control plasma PHE levels by itself and the patients will need to use Kuvan in concert with a low PHE diet. But for many patients responding to Kuvan therapy, an increase in natural dietary protein may be safely done. The amount of natural protein that can be safely increased in the patient using Kuvan must be carefully determined by a metabolic dietician specializing in PKU disease.

Fairview Specialty Pharmacy Approach

Fairview Specialty Pharmacy is an essential component of the country’s most advanced PKU treatment center: The University of Minnesota Medical Center (UMMC) Department of Advanced Therapies. The Advanced Therapies PKU Clinic uses a multidisciplinary approach to identify responders and non-responders to Kuvan. The members of this multidisciplinary PKU Patient Care Team include a geneticist, genetic counselor, metabolic dietician, nurse practitioner, pediatric neuropsychologist, and a clinical pharmacist. The PKU patient care team works together to provide a comprehensive approach towards treatment of PKU disease and to ensure that each patient is receiving optimal care, adhering to their medical formula diet and medication regimen, remaining in contact with the clinic, and is monitoring PHE levels and growth charts.

Fairview Specialty Pharmacy is the only provider of the START regimen (Sapropterin Therapy Accurate Responsiveness Test), a 4-week, double-blind clinical diagnostic test that allows the UMMC clinicians to determine each PKU patient’s individualized response or non-response to Kuvan.¹² If the patient does not respond to the drug, there is no reason for the patient to continue on costly lifelong Kuvan therapy. It is also important that once a patient has been identified as a responder, and has started therapy, that they continue it at the medically monitored dose. Fairview Specialty Pharmacy’s compliance program helps patients successfully stay on therapy. Fairview has been identified through benchmark data from Biomarin, the manufacturer of Kuvan, as helping patients achieve the highest average Kuvan medication possession ratio in the nation (medication possession ratio is a key measure of compliance).

Fairview Specialty Pharmacy PKU Clinical Program Components

Initial order

When the patient and the health care team agree to a trial of Kuvan, the patient is enrolled in the START program. START is a rigorous program that controls for diet and requires dispensing weekly supplies of active Kuvan or placebo, PKU test kits, and dietary logs. The multi-disciplinary team analyzes laboratory values and Kuvan compliance in relationship to diet. With this program, PKU patients are identified as Kuvan responders or Kuvan non-responders. Patients who are non-responders are prevented from taking a longterm therapy with Kuvan. By preventing Kuvan use in a patient for whom it is not effective, the START program results in an annualized drug cost savings of over \$180,000 for an adult patient weighing 150 pounds.

Ongoing patient management

Determination of the optimal Kuvan maintenance dose in responders is also of importance to minimize excess costs. The Optimizing Plan to Increasingly Maximize Individual Sapropterin Efficacy (OPTIMISE) program is an ongoing multi-disciplinary program that provides ongoing individualized and comprehensive services to our Kuvan patients. The multi-disciplinary team monitors and addresses compliance to both diet and Kuvan. With the OPTIMISE protocol, the UMMC Advanced Therapies PKU Clinic along with Fairview Specialty Pharmacy ensures that Kuvan is effective, is providing valuable outcomes, and is used at the lowest effective dose to maximize nutritional needs but minimize unnecessary costs. At an average wholesale price of \$37.00 per tablet, 1-3 tablets fewer per day represents an annual savings of \$13,500 - \$40,500.

Conclusion

Management of PKU disease, and, specifically, the plasma PHE levels in PKU patients, is challenging and requires the combined efforts of a multi-disciplinary Clinical PKU Team for optimal management. Maintaining plasma PHE levels at 6mg/dL or less is necessary to adequately manage executive functioning and mood management in PKU patients. Implementation of low PHE diet may not achieve goal plasma PHE levels of 6mg/dL or less in many PKU patients. For some of these patients, Kuvan therapy may allow for better maintenance of plasma PHE levels within goal range and may also allow for safe increases in natural dietary protein intake and thereby improve nutrition status in PKU patients.

Fairview Specialty Pharmacy is an essential component of the country's most advanced PKU Treatment Center—The UMMC Advanced Therapies PKU Clinic—providing Kuvan for the START and OPTIMIZE treatment protocols. Because not all patients with PKU will benefit from Kuvan therapy, and Kuvan therapy is a costly drug, it is of utmost importance to correctly identify those patients who will respond to Kuvan, as well as those who will not respond, to optimize each patient's therapeutic dose, and to make these determinations as efficiently as possible. ■

Fairview Specialty Pharmacy provides comprehensive specialty pharmacy services. As part of Fairview Health Services, a nonprofit healthcare system including the University of Minnesota Medical Center, we have expertise across the full spectrum of specialty diseases and provide a personalized approach that builds trust with our patients. We leverage our relationships with clinical experts and key opinion leaders at the University of Minnesota Medical Center and its affiliated Advanced Therapies PKU Clinic.



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