Response to sapropterin hydrochloride (Kuvan®) in children with phenylketonuria (PKU): a clinical trial

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Abstract

Background: Phenylketonuria (PKU) is one of the most common types of inborn error of metabolism. The mainstay of therapy for PKU has been dietary phenylalanine (Phe) restriction. Sapropterin dihydrochloride has been shown to be effective in reducing Phe levels in PKU patients.

Methods: This study was a clinical trial performed in the pediatric endocrine clinic of Imam Reza Hospital, Mashhad, Iran.

Results: All children between 1 and 10 years of age with a diagnosis of PKU whose serum Phe levels were between 120 and 360 μmol/L, in Khorasan Razavi province in the north-east of Iran, were enrolled. Twenty-four patients were enrolled in the study. Intervention: A free diet for 72 h was allowed and then a 20-mg/kg/day dose of Kuvan® was administered. More than 30% reduction in blood Phe levels was described as responsive. Eight patients responded to the loading test and were eligible for the second stage of the study. In this stage, Phe powder in combination with Kuvan was provided. Patients’ serum Phe was measured weekly for 3 months. All eight patients showed Phe tolerance in 3 months, and their serum Phe levels remained within the range.

Conclusions: Treatment with Kuvan can help reduce blood Phe levels in our pediatric PKU population and allows patients to follow a more liberal diet.

Keywords: Kuvan; pediatric; phenylketonuria; sapropterin hydrochloride; tetrahydrobiopterin.

Introduction

Phenylketonuria (PKU) is one of the common types of inborn errors of metabolism [1]. It is due to a deficiency in the phenylalanine hydroxylase (PHA) enzyme or its cofactor tetrahydrobiopterin (BH4) which leads to increased levels of serum phenylalanine (Phe). If left without appropriate treatment, increased Phe levels can cause permanent neurologic and intellectual deficits [2]. Oxidative stress may play a role in these neurologic impairments because Phe reduces antioxidant defense [3, 4]. It is an autosomal recessive disorder with variable incidence among different ethnic groups [5]. Its overall incidence is estimated to be 1 in 25,000 live births. The incidence is greater in some populations; e.g. 1 in 4500 in Ireland [6]. In Iran, the incidence is estimated to be 1 in 8000 live births [7].

In this disorder, the enzyme deficiency results in the inability of the body to metabolize Phe into tyrosine and thus the levels of Phe and its metabolites rise and they accumulate in body fluids [8]. The elevated levels of Phe and its metabolites negatively affect the patient’s cognition. Studies have shown that lower intelligence quotient (IQ) has been associated with higher Phe levels [9]; therefore, any delay in treatment initiation can lead to lower IQ.

So far, the mainstay of therapy in PKU has been the dietary restriction of foods containing Phe. The American College of Medical Genetics and Genomics has recommended that blood Phe levels be maintained in the range of 120–360 μmol/L for life [10].

Sapropterin dihydrochloride (BH4) is a pharmaceutical agent that has received Food and Drug Administration approval for use in PKU patients [11]. A 100-mg tablet of BH4 patented as Kuvan® (BioMarin, CA, USA) is available for use in PKU and hyperphenylalaninemia patients [12, 13]. This drug has been shown to be well tolerated in children and no significant side effects have been reported in the literature [14, 15]. Now, many centers report that they would use Kuvan® for children younger than 4 years old [14, 16]. The introduction of sapropterin hydrochloride has made a great difference in the diet of PKU patients [17].

In this study, we evaluated the responsiveness of our pediatric PKU patients to a loading test of sapropterin. Also, patients’ tolerance to Phe was evaluated for 3 months.
Materials and methods

Settings

This was a clinical trial conducted in the pediatric metabolic clinic of Imam Reza hospital, Mashhad, Iran between February 2017 and May 2018. This hospital is affiliated with the Mashhad University of Medical Sciences and is the pediatric referral center for metabolic disorders in the east of Iran.

The study was registered in the Iranian Registry of Clinical Trials under the code: IRTC2016100230082N1.

Participants

Patients between 1 and 10 years of age with mild PKU (serum Phe level 600–1200 μmol/L at the time of diagnosis) in Khorasan Razavi province were included in the study. The selected patients' serum Phe levels were between 120 and 360 μmol/L while receiving 20–50 mg/kg of dietary Phe under the supervision of a dietician. Each 100 g dietary protein of patients was analyzed by our dietician and the Phe content of their daily foods was determined.

These patients were all diagnosed through a newborn screening program and treatment was implemented soon after diagnosis. Patients were considered ineligible and were not enrolled in the study if they had tetrahydrobiopterin deficiency, serum Phe level less than 600 μmol/dL (mild hyperphenylalaninemia) or more than 1200 μmol/L at the time of diagnosis, or had other symptoms such as fever, malnutrition, kidney disease or liver disease.

The study was approved by the medical Ethics Committee of the Mashhad University of Medical Sciences prior to performance, and all eligible patients signed an informed consent form.

Intervention

Selected patients' serum Phe levels were measured prior to the intervention using the high-performance liquid chromatography (HPLC) method. Then, they were given a 72-h long free normal diet. Serum Phe levels were checked and then a 20-mg/kg dose of Kuvan® was administered and then their Phe levels were measured at 24- and 48-h intervals. Patients whose serum Phe levels were reduced by more than 30% after Kuvan® administration were considered as responsive and were eligible for phase 2 of this trial.

In phase 2 of this study, the responsive cases as described earlier were given Phe powder in combination with Kuvan tablets. Patients were divided into two groups according to their diets' daily Phe content. Those whose diet contained less than 500 mg per day of Phe were given 50 mg daily additional Phe powder in combination with Kuvan and increased weekly until the daily Phe intake was double the baseline level. Those with a dietary Phe content greater than 500 mg per day were given 100 mg additional Phe powder daily and increased weekly until the Phe daily intake was double the baseline level. The Phe level was checked on a weekly basis using the HPLC method.

Cases were regarded as responsive if their Phe tolerance increased 2 times their previous diet and their serum Phe level remained in the acceptable range after 3 months.

Statistical analysis

Data were analyzed using the SPSS software, version 16 (SPSS Institute, Inc., Chicago, IL, USA). Data were presented using descriptive statistics including means, frequency and standard deviations.

Results

Twenty-four patients were enrolled in the study. The mean age of patients was 26.7 ± 18.6 months. 45.8% of patients were male and 54.2% were female.

The mean serum Phe level was 1086 ± 504 μmol/dL (range: 312–1848 μmol/dL) at the beginning of the study after 72 h of free diet.

Figure 1 shows the Phe level changes 24 and 48 h after Kuvan administration.

Phe levels 24 and 48 h after Kuvan administration were 1092 ± 660 μmol/dL (range: 102–1926 μmol/dL) and 1284 ± 648 μmol/dL (range: 198–2202/dL), respectively. Some patients whose Phe levels at the time of diagnosis in
the neonatal period were less than 1200 μmol/dL and were categorized as mild PKU but showed Phe levels more than 1200 μmol/dL during the test were excluded from the study.

Eight patients experienced more than 30% reduction in their Phe levels 24 or 48 h after Kuvan administration. For four patients, the Phe reduction was less than 30%, and 12 patients even experienced an increase in Phe levels.

Those eight patients with more than 30% decrease in serum Phe levels were selected for the second stage of the trial. Their mean age was 26 ± 18 months.

Table 1 shows serum Phe levels in accordance with the additional dietary Phe levels during the second stage of the study.

All eight patients showed Phe tolerance during 3 months.

All eight patients could maintain their blood Phe level in the recommended range (see Table 1).

### Discussion

The current standard treatment for PKU is dietary restriction of the amino acid Phe in order to keep Phe levels in the blood within the recommended range to prevent neurologic sequels. While diet remains the mainstay of therapy, tetrahydrobiopterin was suggested as an adjunctive treatment for PKU patients more than three decades ago [18]. Since then, many studies have evaluated its safety and efficacy in PKU patients [2, 5, 6, 13]. Sapropterin dihydrochloride acts through activating the residual activity of the enzyme PHA [13] and it has been approved to be used in pediatric patients both in America and Europe.

In this study, we evaluated both short- and long-term response to Kuvan in Iranian pediatric PKU patients. To the best of our knowledge, this is the first trial of this drug in Iranian pediatric population. Another study by Setoodeh et al. in 2015 was performed on Iranian pediatric PKU patients, but they just evaluated the short-term response to Kuvan [19].

As shown in Figure 1, a large difference was seen between patients with almost sufficient metabolic control and those without after the short course of administration of Kuvan. This might be probably due to the milder nature of their enzyme deficiency, or maybe there are different mutations and we do not have the patients’ mutation analysis.

Studies have shown that 10–60% of PKU patients are BH4 responsive, and this variation is dependent on different mutations in different populations [20]. Results of our study showed that 33.3% of pediatric PKU patients in Khorasan Razavi, north-east of Iran, were responsive to a loading test of tetrahydrobiopterin. In the study by Setoodeh, this was reported to be 28.3%.

Our study also showed that Kuvan treatment can lower Phe concentrations in the blood of PKU patients, and our eight patients who entered the second phase of the study could maintain their blood Phe levels within the recommended range. Many studies have shown the efficacy of BH4 in increasing Phe tolerance in PKU patients [20–24].

None of our patients experienced significant adverse drug reaction while on Kuvan treatment. One patient showed mild signs of gastrointestinal intolerance like nausea and vomiting. However, skin allergic reactions might happen while taking this medication [25]. This has been reported in patients with zinc deficiency [25].

So, treatment with BH4 seems to be a useful adjunctive treatment in PKU patients, especially in those who are not compliant with their diets.

### Conclusions

Results of the present study show that treatment with sapropterin (Kuvan) may allow some pediatric PKU patients to follow a more liberal diet while maintaining their blood Phe concentrations within the optimal range.

Studies with larger populations of patients and also defining the genotype of patients may help better identify the patients who will benefit from this medication.
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References


