Adherence to tetrahydrobiopterin therapy in patients with phenylketonuria

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**Abstract**

Phenylketonuria (PKU) is an inborn error in phenylalanine metabolism due to deficiency of the enzyme, phenylalanine hydroxylase (PAH). Treatment includes restriction of dietary phenylalanine, and in some individuals, supplementation with the PAH cofactor, tetrahydrobiopterin (sapropterin dihydrochloride). A survey was conducted among patients with PKU who had been prescribed sapropterin to assess reasons for continuing or discontinuing the drug. The primary reason that sapropterin responders discontinued the drug was because of side effects, followed by insufficient reduction of blood phenylalanine and insurance issues. Conversely, those who remained on therapy cited increased tolerance for dietary protein as the main reason for continuation, along with lower blood phenylalanine concentrations and feeling better. This study suggests that adherence to sapropterin therapy is mainly dependent upon the increase in dietary protein allowed when on the drug.

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1. Introduction

Phenylketonuria (PKU) is an inherited disorder of phenylalanine metabolism due to a defect in phenylalanine hydroxylase (PAH). In the presence of a normal diet, neurotoxic amounts of phenylalanine accumulate producing intellectual disability as well as marked hyperactivity, autism and seizures. However, newborn screening for PKU, followed by treatment with a phenylalanine-restricted diet that controls blood phenylalanine concentrations, results in essentially normal intelligence and achievement [1]. Restriction of dietary phenylalanine, while effective in treating PKU, requires significant sacrifice by patients and their families. The diet includes consumption of unpleasant medical food and avoidance of popular high protein foods. During infancy and early childhood, dietary adherence is usually adequate for optimal metabolic control. As individuals with PKU become older, however, dietary adherence becomes more difficult and blood phenylalanine control begins to wane [2,3]. Relaxation of control has been associated with later neuropsychological problems, including learning disabilities, slower reaction times, anxiety, phobias, and a number of other emotional disturbances [4]. Although advances in medical foods and a wider assortment of low protein foods have improved the diet, the required avoidance of foods such as meat, eggs, and dairy that are staples in normal diets remains a major personal and social difficulty for affected individuals.

This problem has led to the search for alternative methods of therapy for PKU. An important alternative is the drug sapropterin dihydrochloride™, a synthetic form of the cofactor for tetrahydrobiopterin (BH4). In responsive individuals a pharmacologic amount of sapropterin stimulates residual PAH activity, producing a reduction in blood phenylalanine and allowing for more dietary phenylalanine, thus alleviating some of the difficulty of the diet. Approximately 50% of affected individuals, usually those with milder forms of PKU, respond to this therapy. These individuals may eat more natural protein, including some foods that previously were avoided; a few can even consume a normal diet [5].

Our clinic has had a policy of offering sapropterin to all individuals with PKU, focusing on those with mild or moderate disease. This policy is similar to that recently published from the Johns Hopkins program [6]. We have recommended remaining on sapropterin to those who respond with at least a 25–30% reduction in blood phenylalanine concentration. However, we began to learn that some of these individuals ceased taking the drug and others did not even complete a trial of the drug to determine responsiveness. Consequently, we conducted a survey to determine the extent of adherence to prescribed sapropterin therapy, and reasons for staying on the drug or discontinuing it.

2. Methods

All individuals with PKU followed at the clinic, or a parent of a minor patient, who had signed forms to receive a free trial of sapropterin were asked to participate in a telephone survey about their experiences with the drug. The telephone survey was approved by our Institutional Review Board.

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Review Board and all participants or a parent provided verbal consent to take the survey. The clinic nutritionists conducted the 12-question interview designed to find out why the patient continued or discontinued sapropterin. Answers were entered into a database and descriptive statistical analyses were performed. Statistical significance was determined using a two tailed t-test to compare the frequency of responses in patients who continued sapropterin therapy versus those who did not.

Patients were classified as having severe, moderate or mild PKU or non-PKU mild hyperphenylalaninemia. Classification was based on a patient’s PAH genotype [7] in the 78% of patients for whom a genotype was available in the medical record and/or dietary phenylalanine tolerance using the criteria that patients with severe PKU tolerated less than 300 mg/day, those with moderate PKU 300–400 mg/day, and those with mild PKU >400 mg/day [7]. The classification of non-PKU mild hyperphenylalaninemia was used only for one patient whose blood phenylalanine concentrations have been below 360 μmol/L on an unrestricted diet and who began sapropterin as an infant through another center.

3. Results

109 individuals with PKU who had ever been prescribed sapropterin or a parent were asked to answer the survey and 86 (79%) completed the survey. Of the 23 patients who did not complete the survey, 10 never started therapy (indicated interest but did not follow through with obtaining or taking the drug), 8 began taking sapropterin but did not complete the trial (either they did not send sufficient blood specimens to determine responsiveness, or they discontinued sapropterin on their own before responsiveness was determined), 4 were non-responders, and 1 was considered a responder but did not remain on sapropterin.

Of the 86 patients who completed the survey, 45 (52%) were considered non-responders to sapropterin. The 41 patients (48%) considered responders were the focus of further questioning about their experience with obtaining or taking the drug. Characteristics of these responders are presented in Table 1. Twenty-nine of the 41 responders (70%) remained on their own before responsiveness was determined), 4 were non-responders, and 1 was considered a responder but did not remain on sapropterin.

Fig. 1 presents the reasons patients continued the drug. Patients who continued sapropterin therapy were more likely to be male and to have a mild or moderate form of PKU. While taking sapropterin, dietary phenylalanine tolerance nearly tripled in continuers but only doubled in those that eventually discontinued ($p = 0.063$). One individual was able to discontinue medical food and 3 others were able to reduce medical food intake.

Table 1: Characteristics of patients with PKU who responded to sapropterin therapy.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Remained on drug</th>
<th>Discontinued drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of sapropterin responders</td>
<td>29</td>
<td>12</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>19.7</td>
<td>19.9</td>
</tr>
<tr>
<td>Age range (years)</td>
<td>0.5–54</td>
<td>3–47</td>
</tr>
<tr>
<td>Male</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>Female</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Experienced side effects</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Severity of PKU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild hyperphenylalaninemia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Mild PKU</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Moderate PKU</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>Severe PKU</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Diet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tolerated more dietary PHE</td>
<td>24</td>
<td>7</td>
</tr>
<tr>
<td>Mean protein intake (SD) before sapropterin therapy (g/day)</td>
<td>11.3 (7.7)</td>
<td>8.8 (1.8)</td>
</tr>
<tr>
<td>Mean protein intake (SD) after sapropterin therapy (g/d)</td>
<td>31.8 (17.4)</td>
<td>17.2 (4.6)</td>
</tr>
</tbody>
</table>

All of the 29 patients who continue to take the drug are prescribed 20 mg/kg/day, which is an average of 9 tablets per day (range 2–18 tablets). Nineteen of these continuers (65%) reported taking sapropterin all of the time while the remaining 10 (35%) reported taking the drug some of the time. The most frequent reason cited for less than complete adherence was forgetfulness, reported by 81% of respondents. Approximately half of the patients report swallowing the tablets and about half crush the tablets and mix them with water, juice, applesauce or pudding. Eight patients (28%) do not always take the tablets with food, contrary to advice.

Eighteen patients reported side effects, many of which were gastrointestinal (stomach pain, nausea, acid reflux, diarrhea and blood in the stool). Three reported having headaches on sapropterin, and one reported hair loss. Eight patients discontinued the drug because of the side effects above. Fig. 1 indicates the reasons given for discontinuation among the 12 patients who discontinued sapropterin. The second most frequent reason for drug discontinuation was that it did not work as well as expected, reported by one third of the discontinuers. Three patients mentioned insurance issues as a reason not to continue. Other reasons included difficulty swallowing pills, too many tablets, anxiety, hyperactivity and personal problems.

Fig. 2 presents the reasons patients continued the drug. Patients were instructed to choose all possible answers. The most frequent reason for continuing therapy, expressed by 22 patients (76%), was the ability to tolerate more dietary protein. Fifteen patients (51%) also stated that reduction in blood phenylalanine was a reason for continuing the drug, but none mentioned this as the sole reason for remaining on the drug. Four patients reported that they felt better on sapropterin but none selected this as the sole reason for staying on therapy. Other reasons for continuing on sapropterin therapy were having a more balanced diet and not having to take as much medical food.
4. Discussion

This survey of patients with PKU who were prescribed sapropterin points out the challenges of maintaining a medication regimen along with adhering to a restricted diet. Taking medications is a multi-step process and requires filling the prescription, understanding the drug regimen, organizing and taking the medication as directed, tolerating any side effects and then continuing the medication over the long-term [8]. This process may break down at any point; 24% of new prescriptions are never filled [9], 50% of patients do not take medication as directed [10], and with statin medication for hypercholesterolemia, for example) 25–50% stop taking the medication after one year and 75% after two years [11]. Thus, the fact that 18/109 (17%) of our patients with PKU who indicated interest in drug therapy either never started the medication or never completed the trial, and that 30% of responders to sapropterin self-discontinued the drug is in line with the experience of adherence to other prescribed medications.

In addition to the limited adherence to drug therapy in general, those with PKU have additional challenges. At a dose of 20 mg/kg/day, adolescents and adults with PKU are required to ingest a large number of tablets (e.g. 20 tablets in a 100 kg patient). This might account not only for discontinuing the medication but also for irregular adherence in some continuers. Although only two of the patients surveyed indicated difficulty taking the medication as a reason to discontinue therapy, our clinical experience is that patients often report difficulty taking such a large number of pills. This could be alleviated by a lower dose. For instance, the usual adult dose of sapropterin in Europe is 0.6–1.0 g/day [Blau, personal communication; 12]. Also, for those who have had to crush pills to mix with fluid, the availability of the powder form of the drug may promote better adherence.

Some adolescents and adults with PKU, even if in they are in good metabolic control, have neuropsychological problems that may interfere with their ability to follow medical recommendations, including executive function deficits that include difficulty planning, organizing and controlling impulses [13]. Some individuals may encounter health system-related problems [14] making access to care or ability to follow medical recommendations difficult. Three respondents in this survey attributed discontinuing sapropterin to having had a change of insurance but in the U.S. a specific support system to help gain access to the drug has been developed. Respondents were most likely to discontinue the drug due to side effects ranging from headaches to gastrointestinal problems.

Overall, the frequency of side effects (18/41 patients or 43%) and type of side effects described by survey responders are similar to experiences previously reported [15,16]. In a 22 week study of patients on sapropterin 39% of subjects experienced mild to moderate adverse events that were considered probably or possibly related to the drug including headaches, pharyngo-laryngeal pain, nasopharyngitis, and gastrointestinal side effects (abdominal pain, nausea, diarrhea and vomiting) [16]. Similarly, in a three year follow-up study of patients on sapropterin, the safety profile indicated that adverse events occurring in more than 5% of the subjects included headache, rhinorrhea, pharyngolaryngeal pain, diarrhea, and vomiting [15].

There is limited data on how often responders to sapropterin continue on therapy. A long-term follow-up survey of patients on sapropterin therapy from several European metabolic centers concluded that only 5/94 (5%) responders discontinued treatment for various causes including pregnancy and poor compliance [18]. However, this was the data reported by the centers rather than directly surveying the patients, calling into question its accuracy. Notably, a long-term study from Germany showed that 18/23 patients who initially responded to sapropterin therapy did not continue on therapy because they failed to show an increase in dietary phenylalanine tolerance. According to the German guidelines, an increase in phenylalanine tolerance as well as a reduction in blood phenylalanine concentration is required in order for physicians to recommend continuation of sapropterin therapy [19].

All patients included in our survey who continued sapropterin mentioned increased protein tolerance as the primary reason for continuation. Continuers were able to tolerate nearly three times more protein when on sapropterin compared to their baseline intakes, while discontinuers were only able to tolerate twice as much protein when they had been adhering to sapropterin therapy. The ability to consume more natural protein was of greater importance to responders than reduction in blood phenylalanine or than feeling better. While no quality of life (QOL) measure was used in our study, previous studies generally have not observed a change in QOL scores in patients taking sapropterin [20,21]; however, in one study QOL improved and was attributed to increased protein and reduced medical food in the diet [22].

Not surprisingly, some of the survey participants (21%) were unsure about whether they were BH4 responsive or not. The trial to determine BH4 responsiveness is not standardized. In the U.S., the most frequently used method is a 4-week trial of 20 mg/kg of sapropterin, with frequent monitoring of blood tests and diet intake [17]. However, patients are instructed to maintain the same diet during the trial period, which is difficult and often very unlikely, especially in older patients who often are not carefully counting phenylalanine or protein intake. Catabolism due to infection or caloric deficit during the trial period as well as missed doses of the drug and frequent blood sampling can discourage patients from completing the trial and complicates the determination of BH4 responsiveness.

5. Conclusions

While the indication on the sapropterin label in the US is to reduce blood phenylalanine in combination with a phenylalanine-restricted diet, this survey indicates that the primary reason individuals with PKU stay on drug therapy is that sapropterin allows them to tolerate more dietary protein, and when this does not occur patients may self-select to discontinue the drug. A second conclusion is that determining responsiveness to sapropterin is not straightforward using the current 4-week sapropterin trial because of the many variables that can affect the blood phenylalanine concentration. These difficulties may be ameliorated by a consistent approach to sapropterin trials, a lower dose or higher concentration of the drug may promote better adherence.

Conflict of interest

The authors have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ymgme.2014.10.013.

References

