Natural protein intake in PKU patients: to estimate or to measure?


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ABSTRACT

Objective: This study investigated which methods patients and parents used to realize the Phe intake and the relationship between the methods applied, age and blood Phe concentration.

Patients and methods: A questionnaire was sent to 327 Dutch Phenylketonuria patients (age 0-29 years) to investigate the method used to realize phenylalanine intake (either by estimation, exact measurement or a combination of both). The mean blood phenylalanine concentration of each individual patient was related to the method reported to be used. Three different age groups (<10, ≥10-15, ≥16 years) were distinguished.

Results: The response of the questionnaires was 73%. In these 188 patients, data of both phenylalanine concentrations and questionnaires could be used. Out of these 188, 75 used exact measurement, 75 estimation and 38 used both methods. The number of patients that estimated phenylalanine intake clearly increased with age. Whatever method was used, an increase in phenylalanine concentrations was seen with age. During childhood exact measurement was used more frequently, while from adolescence on estimation was used more frequently. The method (exact measurement and/or estimation) did not result in statistically different phenylalanine concentrations in any of the three age groups, although blood Phe concentration tended to be lower in adolescence using exact measurement.

Conclusion: The data suggest that estimation and exact measurement of the phenylalanine intake are both reliable methods. Therefore, in addition to exact measurement, patients should be instructed in both methods at an early age, so that both methods can be used adequately at each age.

INTRODUCTION

The treatment of Phenylketonuria (PKU) is based on a Phenylalanine (Phe) restricted diet. This diet consists of two inseparable elements: extensive restriction of natural protein to lower the Phe intake in PKU patients, and supplementation of amino acids other than Phe to achieve a normal intake of protein except Phe.

The communication in the treatment of PKU comprises explaining diagnosis, disorder, treatment and care to the parents and training in practical aspects of dietary management. To translate the amount of Phe (i.e. natural protein) into a meal plan, parents are instructed about the Phe content of food and about the use of scales and measuring cups. Dietary protocols and handbooks recommend weighing all protein containing food products. Exact measurement is stated to be the most reliable method to achieve optimal metabolic control, although studies are not available. In the Netherlands parents are initially instructed to weigh all protein containing food on a scale that reads in grams and learn to use the exchange food lists based on the Dutch Food Composition Table NEVO to vary in protein containing products. In daily practice however, parents and patients may realize Phe intake without scales, i.e. by estimation or a combination of both techniques. Crone et al showed that keeping strictly to the PKU diet without being too rigid is associated with a better metabolic control. Using estimation (or a combination of both estimation and exact measurement) may differentiate between strict and rigid dietary treatment.
Therefore this study aimed to investigate the method applied to realize Phe intake at different ages. We compared blood Phe concentrations of the different age groups using exact measurement, estimating or a combination of both.

**PATIENTS AND METHODS**

All PKU patients detected by neonatal screening, referred to one of the eight university affiliated hospitals, born between September 1974 and 2004 in the Netherlands, were included. In the study the patients were divided into 3 groups based on age: < 10 years, ≥10-15 years and ≥16-29 years of age.

A questionnaire was developed to investigate the daily practice used to realize the Phe intake of the PKU patient. The questionnaire was based on the same theoretical behavioral model used by Crone. The theory of planned behavior described by Ajzen, is often applied in health related studies. This model takes into account the following factors as an explanation of behavior: attitude (positive or negative beliefs and experiences with a certain behavior e.g. estimating or measuring protein containing food), subjective norm (normative beliefs and motivation of the social surroundings, social pressure from significant others to perform- or not to perform- a particular behavior) and perceived behavioral control (the person’s belief as to how easy or difficult performance of the behavior is likely to be). In this study behavior was defined as the methods to realize the Phe intake (i.e. exact measurement, estimation or a combination of both). Exact measurement was defined as the method of realizing Phe intake in daily practice with the use of scales and measuring cups and calculation of the amount of Phe. Estimating was defined as “eyeballing” the amount of protein containing food that can be eaten and estimating the Phe content of the portion that is taken. Less precise pre-measured food such as a glass, a plate or a table spoon was defined equal to estimating. Pre-measured food containing a precise defined amount of food in grams was defined equal to exact measurement. Examples of the questions are given in Table 1. The questionnaire was pre-tested by 5 parents and 5 patients ≥ 16 years of age. The mean time to complete the questionnaire was 15 minutes. The questionnaires were sent out by post with additional information about the purpose of the study. A reminder was sent after 3 weeks. The questionnaires used were sent back within 5 weeks after the first posting. Information was given anonymously with a code to be able to combine with blood Phe concentrations.

The questionnaire was tested for internal consistence (Cronbach’s alpha). In the questionnaire answers could be given or could be recoded to a 5-points scale from 0- 4. Measuring = 0, probably measuring = 1, both = 2, probably estimating = 3 and estimating = 4. The questionnaire contained 20 questions about the social economic background and 30 questions concerning the practice of realizing Phe intake by measuring, estimating or both. Of each individual we calculated the mean score. We classified individuals as follows: a score of <1.5 was equal to measuring, 1.5 – 2.49 to both and > 2.5 to estimating.

To define metabolic control we used the mean of the individual blood Phe concentrations from 2001 - 2003. Thus we avoided a large effect of ad hoc fluctuations.
in blood Phe concentrations, due to illness etc. When less than 10 Phe concentrations were available during this period, patients were excluded. All Phe concentrations were measured quantitatively in blood using ion-exchange liquid amino acid analysers.

Metabolic control was not related to the target ranges as the different participating centers did not apply the same target ranges at time of the study. The Dutch National PKU Steering Committee approved the study and the medical ethical committee of the university affiliated hospitals concluded that their approval was unnecessary because the study consisted only of administration of a questionnaire and the retrospective use of blood Phe concentrations. All eight Dutch university affiliated hospitals agreed to participate.

**Statistics**

Kruskal-Wallis tests (in version 10, 2002 of the statistical program SPSS, Inc., Chicago, IL) were performed to compare the Phe concentrations between groups of patients with the same age who determined their Phe intake either by measurement, estimation or using both methods, and to compare the distribution of the methods in the age groups. An $\alpha < 0.05$ was considered statistically significant.
RESULTS

A total of 327 questionnaires were sent out, six questionnaires did not reach the patient. Of the remaining 321, 73% (n=233) was returned with information given by the (parents of) patients. Of these, 24 questionnaires had significant missing data and were excluded from analyses. Of the remaining 209 questionnaires, data of 21 could not be related to the metabolic control because less than 10 blood Phe concentrations were available.

Mean (SD) blood Phe concentrations in the different groups and the number of patients that used exact measurement, estimation or both methods to realize the Phe intake in patients of different ages are shown in Figure 1. The group consisted of 88 patients <10 years of age, 44 patients of ≥10-15 years of age and 56 patients ≥16 years of age. In the group below 10 years of age 55% reported that they used exact measurement, in the older groups ≥ 10-15 years and over 16 years this was 35% and 20% respectively. In the group under 10 years of age 24% reported that they used estimation, in the older groups ≥10-15 years and ≥ 16 years of age this was 36% and 63% respectively. The distribution of the methods in the age groups (Kruskall-Wallis test) was significantly different (p < 0.001).

Figure 1. Blood Phe concentrations in the different groups and the number of patients that used exact measurement, estimation of both methods to realize the phenylalanine intake in patients of different ages.
Phe concentration rose with age irrespectively the method used. In all age groups patients used exact measurement or estimation rather than a combination of both methods. The method used did not result in significant differences in the mean Phe concentrations in any age group, although in the group ≥10-15 years, exact measurement tended to result in lower blood Phe concentrations.

**DISCUSSION**

The most important findings of the present study were that in all age groups the methods did not result in statistically differences in mean Phe concentrations, although in the group ≥10-15 years, exact measurement tended to result in lower blood Phe concentrations.

From the results it appears that there was a gradual change from exact measurement at young age to estimation at later age. At the first confrontation of the parents with PKU they have to learn how to manage the treatment and feel comfortable with clear instructions. When confidence in the treatment and their own capabilities grow, they are likely to develop other methods. Initially measuring with scales and calculating the amount of Phe, parents and patients may develop the skills necessary to measure without scales and calculator. However, at the same time 20% of the adult patients answered that they continue to use the exact measurement.

Differences in target ranges may have influenced differences in resulting blood Phe concentrations. However at the time of the studied period national guidelines were developed. The nationally agreed target ranges were close to the different targets applied in the eight institutes, and not likely expected to influence the study results largely. Severity of the disease might have influenced the choice for a certain method to realize Phe intake. In the study differences in Phe tolerance (as measure of severity of disease) was not taken into account as it was impossible to match individual figures about the Phe intake as these data were not available anonymously. In day to day practice we find patients realizing Phe intake with different methods, irrespective their severity of the disease.

To assess whether findings were subject to selection bias, we compared mean blood Phe concentration in the participating patients with the mean blood Phe concentrations in comparable age groups of previous national Dutch studies, showing comparable mean blood Phe concentrations in the same age groups⁵,⁸.

Phe concentrations were not related to the method of realizing Phe intake within any age group, but in the age group 10-15 years there was a tendency to lower blood Phe concentrations in the group that measured (Figure 1). This could suggest that in this age group the start of experimenting with estimating results in a tendency to higher blood Phe concentrations, rather than a consequence of estimating itself. In contrast, this difference in blood Phe concentration is clearly smaller in adults, in this age group the combination of both methods resulted in a tendency to lower blood Phe concentrations. This would- as a consequence- suggest the importance of being capable to use both methods. In general, we see that beyond childhood a significant percentage of the patients show higher mean blood Phe concentrations⁹,¹¹. This
study tried to contribute to the puzzle how to influence the phenomenon of rising blood Phe concentrations of adolescent and adult patients. The clinical relevance of treatment at the time of diagnosis and throughout childhood is unquestionable and most guidelines also agree that dietary treatment of PKU should be continued throughout adult life. Weglage and Burgard described that psychosocial problems seem to arise in adolescent and adult patients and speculated that this may be associated with the burdensome diet. Life of adolescents changes completely with regard to school, sports, societies, and the importance of peer groups both in healthy adolescents and adolescents with chronic diseases. In healthy adolescents, responsibilities are transferred from the parents to the adolescents themselves. In chronic diseases, not only normal responsibilities are transferred, but also responsibilities and activities specific for the disease, e.g. medicine, dietary instructions and diet. As a consequence adolescents need time to get experienced with their responsibilities in general and with regard to their disease. Measuring without scales can make life with PKU less different from normal. Simplifications in dietary treatment can contribute to a better compliance.

CONCLUSIONS

This study showed that exact measurement of Phe intake compared to estimating Phe intake, is not clearly related to a lower mean blood Phe concentration. It can be more attractive for patients/parents to be able to realize Phe intake by “eyeballing” rather than by exact measurement, being compliant, but not too rigid. In the dietary treatment it is of importance that after initial instruction in exact measurement, both methods (i.e. to estimate and to measure) are taught to realize Phe intake early in life, so that both can be used adequately and patient and parents can choose the method with which they are most comfortable with in different situations.

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References