Phenylketonuria: tyrosine supplementation in phenylalanine-restricted diets

Francjan J van Spronsen, Margreet van Rijn, Jolita Bekhof, Richard Koch, and Peter GA Smit

ABSTRACT  Treatment of phenylketonuria (PKU) consists of restriction of natural protein and provision of a protein substitute that lacks phenylalanine but is enriched in tyrosine. Large and unexplained differences exist, however, in the tyrosine enrichment of the protein substitutes. Furthermore, some investigators advise providing extra free tyrosine in addition to the tyrosine-enriched protein substitute, especially in the treatment of maternal PKU. In this article, we discuss tyrosine concentrations in blood during low-phenylalanine, tyrosine-enriched diets and the implications of these blood tyrosine concentrations for supplementation with tyrosine. We conclude that the present method of tyrosine supplementation during the day is far from optimal because it does not prevent low blood tyrosine concentrations, especially after an overnight fast, and may result in largely increased blood tyrosine concentrations during the rest of the day. Both high tyrosine enrichment of protein substitutes and extra free tyrosine supplementation may not be as safe as considered at present, especially to the fetus of a woman with PKU. The development of dietary compounds that release tyrosine more slowly could be beneficial. We advocate decreasing the tyrosine content of protein substitutes to \( \approx 6\% \) by wt (6 g/100 g protein equivalent) at most and not giving extra free tyrosine without knowing the diurnal variations in the blood tyrosine concentration and having biochemical evidence of a tyrosine deficiency. We further advocate that a better daily distribution of the protein substitute be achieved by improving the palatability of these products. Am J Clin Nutr 2001;73:153–7.

KEY WORDS  Phenylketonuria, PKU, tyrosine, protein substitute, amino acid supplementation, tyrosine supplementation, maternal PKU

INTRODUCTION

Normally, tyrosine is a nonessential amino acid synthesized from phenylalanine. Tyrosine is incorporated into all proteins and is a precursor of thyroxine, melanin, and the neurotransmitters dopamine and norepinephrine. Persons with phenylketonuria (PKU) cannot synthesize tyrosine from phenylalanine because of a severe deficiency of the hepatic enzyme phenylalanine hydroxylase (phenylalanine 4-monoxygenase). Therefore, in these persons, tyrosine is an essential amino acid. Left untreated, PKU results in restriction of natural protein to an amount that meets the phenylalanine need for protein synthesis and supplementation with a protein substitute to meet the total protein need. The protein substitute consists of an amino acid mixture that lacks phenylalanine or a protein hydrolysate that contains very little phenylalanine.

From the start of PKU treatment in 1954, tyrosine was added to the protein substitutes to a content equal to that found in human milk (2). Tyrosine enrichment of the protein substitutes compensates for the phenylalanine normally converted into tyrosine was reported as early as 1961 (3). At present, the tyrosine enrichment of the different protein substitutes varies greatly, resulting in a tyrosine content of 4.6–14.7% by wt (4.6–14.7 g/100 g protein equivalent; Table 1).

Recently at our center, a pregnant woman with PKU had plasma tyrosine concentrations that were clearly increased on various occasions, sometimes even >200 µmol/L, even though she consumed her total daily amount of protein substitute in 3–4 equal parts. Note that reported reference values of tyrosine are always between 35 and 102 µmol/L (7–10). This finding urged us to address the following question: is such a large tyrosine enrichment in the protein substitute for the treatment of PKU and maternal PKU really needed?

Especially in the treatment of maternal PKU, some authors advise extra free tyrosine in addition to the use of tyrosine-enriched protein substitutes (5, 11–18). Again, we question whether this is needed, and even safe, especially for fetuses of women with PKU.

In this article, we address these questions about tyrosine supplementation in PKU and maternal PKU. We first discuss tyrosine metabolism in healthy individuals. Second, we address blood tyrosine concentrations in PKU patients during low-phenylalanine, tyrosine-enriched diets. Third, we discuss the implications of these tyrosine concentrations in blood for possible tyrosine deficiency and toxicity, and, as a consequence, for tyrosine supplementation in (maternal) PKU. We conclude with theoretical and practical considerations for achieving better tyrosine supplementation.

1 From the Department of Metabolic Diseases, Beatrix Children’s Hospital, University Hospital of Groningen, Groningen, Netherlands, and the Division of Medical Genetics, Children’s Hospital Los Angeles.

2 Address reprint requests to FJ van Spronsen, Department of Metabolic Diseases, Beatrix Children’s Hospital, University Hospital of Groningen, PO Box 30.001, 9700 RB Groningen, Netherlands. E-mail: f.j.van.spronsen@bkk.azg.nl. Received May 1, 2000. Accepted for publication July 18, 2000.
Table 1
Tyrosine content of protein substitutes commonly used in the treatment of phenylketonuria

<table>
<thead>
<tr>
<th>Company, reference, and protein substitute</th>
<th>Tyrosine content % by wt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mead Johnson, Evansville, IN (4)</td>
<td>5.4</td>
</tr>
<tr>
<td>Lofenolac</td>
<td></td>
</tr>
<tr>
<td>Phenyfree</td>
<td>4.6</td>
</tr>
<tr>
<td>Milupa, Friedrichsdorf, Germany (5)</td>
<td>6.8</td>
</tr>
<tr>
<td>PKU-1</td>
<td></td>
</tr>
<tr>
<td>PKU-2</td>
<td>7.4</td>
</tr>
<tr>
<td>PKU-3</td>
<td>14.7</td>
</tr>
<tr>
<td>PKU-1-mix</td>
<td>9.1</td>
</tr>
<tr>
<td>Nutricia, Zoetermeer, Netherlands (5)</td>
<td></td>
</tr>
<tr>
<td>Phenylon AM</td>
<td>12.5</td>
</tr>
<tr>
<td>Phenylon-1 mix</td>
<td>12.3</td>
</tr>
<tr>
<td>Phenylon-2 mix</td>
<td>12.3</td>
</tr>
<tr>
<td>Phenylon-3 mix</td>
<td>12.3</td>
</tr>
<tr>
<td>Phenylon-Formula</td>
<td>12.6</td>
</tr>
<tr>
<td>Ross Laboratories, Columbus, OH (6)</td>
<td></td>
</tr>
<tr>
<td>Phenex-1</td>
<td>10</td>
</tr>
<tr>
<td>Phenex-2</td>
<td>10</td>
</tr>
<tr>
<td>Scientific Hospital Supplies (SHS),</td>
<td></td>
</tr>
<tr>
<td>Liverpool, United Kingdom (5)</td>
<td></td>
</tr>
<tr>
<td>PKU-Aid XP</td>
<td>11.7</td>
</tr>
<tr>
<td>Albumaid XP</td>
<td>12.6</td>
</tr>
<tr>
<td>Maxamaid XP</td>
<td>10.8</td>
</tr>
<tr>
<td>Maxamun XP</td>
<td>10.8</td>
</tr>
<tr>
<td>Flexy-10</td>
<td>11.6</td>
</tr>
<tr>
<td>Analog</td>
<td>11.0</td>
</tr>
</tbody>
</table>

g/100 g protein equivalent.

Normal Tyrosine Metabolism

In vivo metabolic studies that focused on tyrosine metabolism in healthy humans are scarce (19–21) and data on recommended intakes and deficiency in humans concern the combination of phenylalanine and tyrosine (22–24). Gleaser et al (19) showed that plasma tyrosine concentrations increased to a mean of 203 µmol/L in response to large doses (up to ≈10 g) of extra tyrosine in healthy individuals. The results of a pilot study with 13C-tyrosine conducted by Cortiella et al (20) showed that tyrosine oxidation doubles the rates of phenylalanine oxidation and hydroxylation, but no data were presented on the relation between tyrosine oxidation and the subjects’ nutritional condition (fasting or nonfasting). The studies of Basile-Filho et al (24) made clear that both nutritional condition and phenylalanine intake (generous, intermediate, or low) influence the rates of phenylalanine hydroxylation and tyrosine oxidation as well as plasma phenylalanine and tyrosine concentrations. Basile-Filho et al’s studies were hampered, however, by the fact that all individuals had low tyrosine intakes. Thus, it is still unclear what the metabolic system does with tyrosine from dietary sources. The results of in vitro studies in rat liver and in vivo studies in healthy adult humans suggest that the metabolic fates of tyrosine from phenylalanine and dietary sources might be different (21, 25).

Reference values of tyrosine concentrations in plasma vary between 35 and 102 µmol/L for different age groups and sexes when measured after an overnight fast (7). In the nonfasting condition in healthy young adults, plasma tyrosine concentrations vary between 61 and 99 µmol/L (8–10). Studies of diurnal variations in amino acid concentrations in healthy adults with normal intakes of dietary protein showed that plasma tyrosine concentrations decrease during the evening and early nighttime. Concentrations are lowest between 0200 and 0400 and highest in the nonfasting state (26, 27), but this pattern changes in cases of deficient phenylalanine and tyrosine intakes.

Obligate heterozygotes for phenylalanine hydroxylase deficiency (eg, parents of children with PKU) have normal plasma tyrosine concentrations both after an overnight fast and postprandially (28), suggesting that these individuals do not carry a risk of tyrosine deficiency. The phenylalanine hydroxylating system is active from early in fetal life (29, 30), although the importance of this system for the fetus may be questioned (31).

Tyrosine Concentrations in Treated PKU Patients

Studies of treated PKU patients conducted by Güttler et al (F Güttler, ES Olesen, E Wamberg, unpublished observations, 1968) and Brouwer et al (32) showed that overnight, fasting serum tyrosine concentrations can be clearly below reference values. Koepp and Held (33) showed that serum tyrosine concentrations in treated PKU patients are normal at noon compared with those in healthy persons. More recent studies in treated PKU patients underlined this decrease in plasma tyrosine concentrations after an overnight fast (34–37). It was further shown that plasma tyrosine concentrations decrease even more when breakfast is skipped (36). This may be caused by the lack of tyrosine intake over the previous hours combined with the decreased hydroxylation rate of phenylalanine into tyrosine in PKU patients (38).

Two studies reported individual daily fluctuations in plasma tyrosine concentrations in patients in whom the individually tailored intake of natural protein and tyrosine-enriched protein substitute was distributed either equally or unequally throughout the day (36, 37). A third study presented data on plasma tyrosine concentrations after extra free tyrosine was given in addition to the tyrosine-enriched protein substitute (14). The first study showed that an equal distribution of the protein substitute resulted in both intralaboratory and interindividual variations in tyrosine concentration (36). Tyrosine values remained low in 3 of the 9 patients studied, became normal in 2 of 9, and were clearly elevated in 4 of 9. Additionally, postprandial plasma tyrosine concentrations were always higher than preprandial concentrations (36). The second study showed that unequal distributions of the total daily natural protein intake and protein substitute (n = 12) resulted in even larger intralaboratory fluctuations in tyrosine concentrations (37). In that study, postprandial plasma tyrosine concentrations above the reference range were observed in >80% of the patients, the highest being 340 µmol/L. The third study showed that giving extra tyrosine to 5 women with PKU in addition to an amino mixture with either a low or a much larger tyrosine content resulted in plasma tyrosine concentrations up to 200 µmol/L (14). In summary, this implies that not only very low but also high to very high plasma tyrosine concentrations can occur frequently in PKU patients.

Implications of Tyrosine Concentrations for Deficiency, Toxicity, and Tyrosine Supplementation

In a discussion of tyrosine supplementation, knowledge of the problems that may be related to both tyrosine deficiency and tyrosine toxicity is needed. In both deficiency and toxicity, a...
phenylalanine and tyrosine to deficiency in the brain is accepted, normalizing the ratio between brain of PKU patients. If one of these hypotheses on dopamine increased plasma tyrosine concentrations may be beneficial to the dopamine deficiency in the brain, it could be hypothesized that concentrations in PKU patients, and the hypotheses concerning (49). With this lack of a clear toxic effect of high plasma tyrosine ataxia, convulsions, and cerebral atrophy, there is no clear rela-
tion and no relation between the eye problems and the plasma tyrosinemia type I reported eye problems but no mental retardation. In tyrosinemia type III, which has been associated with mental retardation, corneal lesions, and skin disease, it is recom-
ned that tyrosine concentrations >200 µmol/L and aim at more or less nor-
mal phenylalanine-tyrosine ratios. Plasma tyrosine concentrations are low during the night (when plasma phenylalanine concentrations are the highest) and show large fluctua-
tions during the day (when plasma phenylalanine concentrations decrease, sometimes even dropping below normal plasma concentrations) (53). Consequently, especially in the treatment of maternal PKU, we should not only keep plasma phenylalanine concentrations as normal as possible and prevent low plasma tyrosine concentrations, but also prevent maternal plasma tyrosine concentrations >200 µmol/L and aim at more or less nor-
mal phenylalanine-tyrosine ratios. Therefore, it must be ques-
tioned whether the present practice of advising large amounts of tyrosine within the tyrosine-enriched protein substitute or as free tyrosine is safe, especially to pregnant women with PKU. Various approaches for improving tyrosine supplementation are discussed in the next section.

IS THERE AN OPTIMAL MODE OF TYROSINE SUPPLEMENTATION? THEORETICAL AND PRACTICAL CONSIDERATIONS

Natural proteins contain ~4% tyrosine and 4.5–5% phenylala-
nine, of which 67–90% is converted into tyrosine in healthy indi-
viduals according to the results of in vitro liver studies (11). According to these calculations, protein substitutes should con-
tain some 7–8.5% tyrosine by wt (ie, 7–8.5 g tyrosine/100 g protein equivalent) if we aim at tyrosine enrichment, which covers the lack of tyrosine, the reduced amount of natural protein, and the lack of conversion of phenylalanine into tyrosine in persons with PKU. More recent in vivo studies of whole-body phenylalanine-tyrosine fluxes, however, showed that only 27–41% of dietary phenylalanine is converted into tyrosine during the first 5–8 h after a generous dietary phenylalanine intake (24, 54). This suggests that a tyrosine content in the protein substitute of ≈6% by wt at most may be more adequate. Theoretically, it is possible that larger amounts of phenylalanine are converted into tyrosine over a longer period, suggesting a greater need for tyrosine, but the results of a recent study by Bross et al (55) suggest that the need for tyrosine in PKU patients is <6% of the total protein intake. One of the reasons for a lower need for tyrosine may be that tyrosine is not only used to synthesize melanin, neuroactive compounds, and proteins including thyroxine, but also oxidized. Another source for establishing the tyrosine content of protein substitutes might be the recommended dietary allowances as published by the National Research Council (22). These, however, concern the combined intake of phenylalanine and tyrosine and therefore are of no help in establishing the optimum tyrosine content of the protein substitutes used in PKU.

In addition to these considerations, Herrmann et al (56) showed that too much of a protein substitute at one time results in an ineffective use of the amino acids. Thus, provision of both a tyrosine-enriched protein substitute and extra free tyrosine may not be optimal because it results in very high plasma tyrosine concentrations and increased oxidation rates without preventing low overnight fasting plasma tyrosine concentrations. Therefore, the ideal tyrosine supplement should be based on 2 kinds of tyrosine: the amount of tyrosine normally ingested as natural protein and a slow-release tyrosine compound. This slow-release compound should cover the amount of tyrosine normally synthesized from dietary phenylalanine and should resemble the natural conversion of phenylalanine into tyrosine, especially during the night.

Future studies in patients with PKU should focus on various aspects of tyrosine metabolism, including the effects of different means of supplying the protein substitute on the plasma concentrations of tyrosine and other amino acids and the rates of protein synthesis and oxidation during various nutritional conditions. Other methods of supplementation should be considered, including distribution of the total daily amount of protein substitute consumed over >4 times/d. Such a regular intake of the protein substitute necessitates good compliance, however, which may not be achieved in PKU patients (57) and may be even lower in maternal PKU because of emesis gravidarum. One of the major causes of noncompliance by patients with PKU is the poor palatability of the protein substitutes, which is caused by a combination of various compounds, including tyrosine (58). This may be another reason to decrease the tyrosine content of the protein substitutes to ≈6% by wt at most.

In conclusion, the present mode of tyrosine supplementation in persons with PKU is far from optimal. The tyrosine enrichment of the protein substitutes is often greater than is necessary. Both the large tyrosine enrichment and the extra free tyrosine may not be as safe as presently believed, especially to the fetus of a woman with PKU, because these do not prevent low plasma tyrosine concentrations and result in largely increased plasma tyrosine concentrations. Therefore, it is worth trying to decrease the tyrosine content of the protein substitutes to ≈6 by wt (6 g/100 g protein equivalent) at most, part of the tyrosine being a compound from which tyrosine is released slowly. We do not advocate use of extra free tyrosine without knowledge of the diurnal variations in plasma tyrosine concentrations and biochemical evidence of a tyrosine deficiency. Improving the palatability of the protein substitutes may be necessary to achieve a better daily distribution of these products.

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