Protein substitute requirements of patients with PKU on BH4 treatment: a systematic review and meta-analysis

Fatma Ilgaz1, Cyril Marsaux2, Alex Pinto3, Rani Singh4, Carmen Rohde5, Erdem Karabulut1, Hülya Gökmen-Özel1, Mirjam Kuhn2, and Anita MacDonald3

1Hacettepe University; 2Danone Nutricia Research; 3Birmingham Women’s and Children’s Hospital; 4Emory University; 5University of Leipzig

Background

- The traditional treatment for PKU is a Phe-restricted diet.
  - Supplementation with a Phe-free/low-Phe protein substitute (medical formula) is necessary to meet age-appropriate protein requirements for growth.1,2
  - Protein substitutes are essential to provide tyrosine, micronutrients & essential fats, to improve Phe tolerance and optimize metabolic control.1,3-6
- Although successful, the PKU diet is a substantial burden for patients and their families.7
- Pharmaceutical treatment with synthetic tetrahydrobiopterin (BH4), cofactor of phenylalanine hydroxylase, allows 20-50% of patients to relax their diet.8-13
- However, the need for protein substitute with long-term BH4 treatment has not been thoroughly studied and few dietary protocols are available to guide the adjustments of protein equivalent intake from protein substitute with BH4 therapy.14

Aim

- To systematically review protein substitute usage with long-term BH4 therapy.
- To define criteria for continued protein substitute administration with BH4.

Methods

- Electronic databases (including Medline, Embase, SciSearch and BIOSIS Previews) were searched for articles published between January 2000 and March 2020.

Results

1. Study Characteristics

- n = 306 long-term BH4 responders
- Age at BH4 initiation: 5 mo – 18 y
- Therapy duration: 3 mo – 6 y

References: 1Van Wegberg et al. 2017; 2MacDonald et al. 2020 (Orphanet J. Rare Dis.); 3MacDonald et al. 2020 (Clinical Pediatric Dietetics);
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Results

### Change in dietary Phe intake

Consistent increase in Phe intake and intake of natural protein (not shown).

### Change in protein equivalent intake from protein substitute

Consistent reduction in protein equivalent intake from protein substitute.

Read the full publication: Ilgaz et al. 2021, https://doi.org/10.3390/nu13031040
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Results

n = 306 long-term BH4 responders

- 51% stopped PS
- 49% continued PS

n = 149 still on protein substitute

- 28%: reduced dose of PS
- 14%: same dose of PS
- 58%: change in dose not reported

4 Protein substitute usage

Main reason for continuing protein substitute with long-term BH4 therapy

Not able to increase dietary Phe / natural protein intake sufficiently without compromising metabolic control.

5 Secondary outcomes

Micronutrient status
Decrease in vit D, B₁₂, folic acid, iron, calcium intakes & serum zinc, iron, folic acid and vit B₁₂, in some, but not all, studies.

Growth
Weight- and height-for-age z-scores remained within the normal range; linear growth improved in 2 studies.

Metabolic control
Mean/median blood Phe levels remained in age-specific target ranges in most subjects.

Recommendations

- BH4 responsiveness requires careful assessment.
- Expected final Phe tolerance should be increased by ≥100% of baseline (provided baseline natural protein intake is below safe levels of protein intake; otherwise, improved blood Phe control as alternative goal).
- Monitoring: At least 75% of blood Phe levels should remain within target therapeutic range and more than 100% of original prescription of Phe intake should be maintained (unless safe levels of protein intake already met).
- Protein equivalent intake from protein substitute should be reduced gradually in parallel with any increase in natural protein with the goal to at least provide safe levels of protein intake. If that is not achieved, protein substitute prescription should be increased, and also during events of increased protein requirements (e.g., rapid growth, illness, etc.).
- Micronutrient status should be monitored.
- Quality of protein: Natural protein should be consumed from various sources.

Take Home Message

PKU patients

BH4-responsive 20-50% of PKU patients (mainly milder forms)

Long-term BH4 use

BH4-responsive

51% CAN STOP PROTEIN SUBSTITUTE

49% STILL NEED PROTEIN SUBSTITUTE

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