Recommendations about the use of tetrahydrobiopterin (BH4) in phenylketonuric (PKU) patients in Switzerland

Swiss Group for Inborn Errors of Metabolism (SGIEM)*

BH4 is the natural cofactor of the enzyme phenylalanine (Phe) hydroxylase, which is deficient in PKU patients. Since 1999, several studies have shown that some PKU patients may benefit from BH4 treatment[1), 2), 3), 4)]. There is currently no international consensus about the clinical and biochemical criteria for assessing BH4 responsiveness and for treating PKU patients. First hand clinical experience with BH4 treatment has been gained in Swiss metabolic centers, as a limited number of PKU patients have been treated with BH4 since 2003. Due to the recent introduction of Sapropterin (Kuvan®) on the Swiss market by Merk-Serono, BH4 therapy has become far more expensive than dietary treatment. In order to provide a reasonable and homogenous approach to the treatment of PKU patients with BH4 in Switzerland, the Swiss Group for Inborn Errors of Metabolism (SGIEM) has reached consensus on criteria for treatment and responsiveness assessment, based on the current knowledge in the field, the experience of the Swiss centers, and the published swiss recommendations for the treatment of PKU and hyperphenylalaninemia.[5)]

The SGIEM recommends the use of BH4 in PKU patients under the following conditions:

1. BH4 oral treatment should be considered only in PKU patients requiring dietary treatment (blood Phe level > 400 µmol/L); it should not be considered in patients with mild hyperphenylalaninemia (blood Phe level < 400 µmol/L under free diet in the first 10 years; blood Phe level < 600 µmol/L under free diet after 10 years).[5)]
2. BH4 should be used in PKU patients without age restriction (off-label use under 4 years of age). Assessment of BH4 responsiveness is recommended either at diagnosis (newborn screening) or once individual Phe tolerance has been defined, which may be best before weaning (4–5 months of age).
3. Only fully responsive PKU patients should be considered for treatment. Fully responsive patients should reach a Phe intake corresponding to the minimum safe protein intake for age (according to DACH Reference values) under BH4. Partially responsive patients exist, who increase their Phe tolerance by several hundreds mg of phenylalanine but are not on a free diet under BH4 treatment. These patients are, at present, not candidates for BH4 treatment due to the limited benefit in relation with the high cost of the medication.
4. Assessment of BH4 responsiveness should be done in the following way:
   a. Therapeutic trial with BH4 10 mg/kg/day (1x/day) for 4 weeks, regardless of baseline blood Phe levels.
   b. Blood Phe controls 2x/week; daily dietary protocol for Phe intake calculation.
   c. Progressive increase of Phe intake up to a level corresponding to the minimum safe protein intake for age by the end of the 4 week trial. The additional Phe intake should be given as milk powder, to mix with the usual amino-acid mixture. No other protein-rich food should be introduced before establishing patient's responsiveness.
   d. Responsive patients should keep blood Phe levels below the recommended thresholds for age while receiving a diet corresponding to the minimum safe protein intake for age (blood Phe < 300 µmol/L between 0 and 2 years; < 400 µmol/L under 10 years; 600 µmol/L above the age of 10 years).[5)] If blood Phe levels increase above the recommended safe thresholds after the first steps of increased Phe intake, in the absence of illness or other catabolic factors, the patient is considered non-responsive and the trial can be stopped.
   e. Responsiveness, defined as above, should be sustained during at least three months to confirm continuation of BH4 treatment (this observational period can be prolonged in case of intercurrent illness).
5. A standard dosage of 10 mg/kg/day administered once daily is recommended in children, with a maximum total dose of 800 mg/day in adults. In our experience, there is so far no proven advantage that higher doses are effective to obtain full responsiveness.
6. PKU women during pregnancy need a strict control of their blood Phe level in order to prevent severe embryofoetopathy (maternal PKU); there are not enough data on the use of BH4 in pregnancy in responsive patients and its use is therefore not recommended. However, in patients with major problems in maintaining blood Phe levels in the safe range under dietary control, the administration of BH4 may present fewer risks than elevated Phe levels and should therefore be considered for treatment.
7. The SGIEM recommends limitation of BH4 prescription to the metabolic specialists in the University Hospitals in Switzerland, as for other highly expensive treatments for inborn errors of metabolism.
8. The SGIEM recommends that pharmacoeconomical studies should be performed to address the economic and ethical issues linked to the cost/benefit of the medication.

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