

Thomas Opladen · Marcel Zurflüh · Ilse Kern
Luca Kierat · Beat Thöny · Nenad Blau

Severe mucitis after sublingual administration of tetrahydrobiopterin in a patient with tetrahydrobiopterin-responsive phenylketonuria

Received: 2 November 2004 / Accepted: 12 January 2005 / Published online: 22 February 2005
© Springer-Verlag 2005

Tetrahydrobiopterin (BH₄) is the cofactor for phenylalanine hydroxylase (PAH) and is essential to treat different forms of hyperphenylalaninaemia, i.e. patients with defects in the biosynthesis of BH₄, but also in the PAH gene [1, 4, 5]. Responsiveness of mutant PAH to BH₄ administration relies on a chemical chaperon effect of BH₄ preventing PAH from protein misfolding and inactivation [6], but several other mechanisms may also be involved [2]. Recently, we reported that sublingual administration of BH₄ tablets in a single control person resulted in 58%–67% higher plasma BH₄ concentrations than the usual oral route [3]. Drawbacks included rapid decomposition of tablets, acidic taste, and increased salivation. Since sublingual application could reduce therapy costs, orange flavoured artificially sweetened BH₄ pastilles were tested on four healthy volunteers and a child with mild phenylketonuria (PKU).

BH₄ (Schircks, Switzerland) was administered to four healthy male volunteers (age 28–57 years) on 2 subsequent days either as tablets (50 mg) or pastilles (100 mg, containing 5 mg aspartame and orange aroma) with a 1 week wash-out between the two trials. Blood was collected before, and 1, 2, 3, and 4 h after administration. An 8-year-old patient with mild PKU

(genotype P281L/R261Q) who was already on regular BH₄ therapy was treated with BH₄ pastilles (sublingually, 12 mg/kg/day; bid) in addition to P-AM 2 formula for 2 weeks. Written consensus was obtained from the family.

In the four healthy male volunteers, total biopterin values before and up to 4 h after oral and sublingual administration were compared (Fig. 1A). No statistically significant difference between oral and sublingual administration was observed. Pterin concentrations increased after both oral and sublingual administration, reflecting instability of BH₄ in blood. The ratio of pterin to cumulated biopterin and pterin ranged between 22.8% and 33.5%. Summing biopterin and pterin instead of total biopterin did not alter the ratio between oral and sublingual administration (data not shown).

Changing from standard therapy to sublingual administration in a child with mild PKU resulted in almost unchanged plasma phenylalanine concentrations (Fig. 1B). After 2 weeks of twice daily sublingual BH₄ administration, the patient complained of a painful prickling sensation at the tip of the tongue. He nevertheless continued the treatment for a further 10 days, moving the tablets in his mouth from one side to the other, which resulted in severe mucitis. His condition normalised rapidly upon discontinuation of the sublingual form. No mucitis appeared in healthy volunteers.

A clinical trial with sublingual BH₄ in a patient with mild PKU failed despite pharmacological effectiveness on blood phenylalanine levels because of an adverse pastille-related side-effect. Formulation of buffered tablets approaching neutral pH and further investigations on BH₄ metabolism and pharmacokinetics are needed.

The first two authors contributed equally to this work.

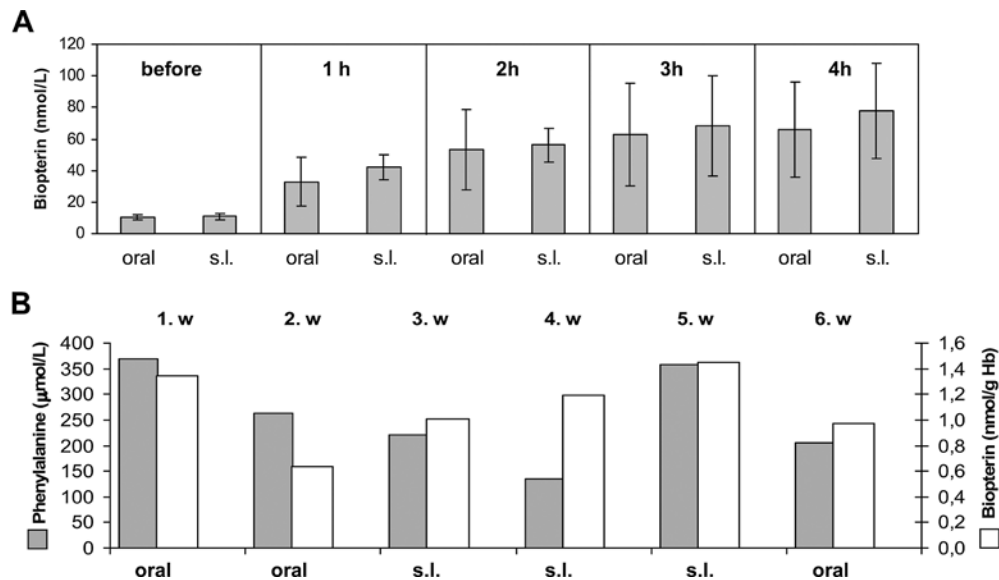
T. Opladen · M. Zurflüh · L. Kierat · B. Thöny · N. Blau (✉)
Division of Clinical Chemistry and Biochemistry,
University Children's Hospital, Steinwiesstrasse 75,
8032 Zurich, Switzerland
E-mail: nenad.blau@kispi.unizh.ch
Tel.: +41-1-2667544
Fax: +41-1-2667169

T. Opladen
Division of Paediatric Neurology,
Department of Paediatrics, University Hospital,
Aachen, Germany

I. Kern
Division of Metabolism, Department of Paediatrics,
University Hospital, Geneva, Switzerland

Acknowledgements The authors thank the patient and his family for their exemplary participation. This work was supported by the Swiss National Science Foundation grant no. 3100-066953.01. Thomas Opladen received a research grant from the Aachen Medical Faculty and support from the "Sanitätsrat-Dr.-Emil-Alexander-Huebner-und Gemahlin-Stiftung".

Fig. 1 **A** Comparison of total plasma biopterin levels (median \pm SD) after oral or sublingual administration of BH₄ (2 mg/kg) in four healthy volunteers at different time points. **B** Dried blood spot phenylalanine (*solid squares*) and biopterin (*open squares*) measured 3 h after oral (15 mg/kg) or sublingual (12 mg/kg) administration of BH₄ in a patient with mild PKU (*s.l.* sublingual)



References

- Bernegger C, Blau N (2002) High frequency of tetrahydrobiopterin-responsiveness among hyperphenylalaninemias: a study of 1919 patients observed from 1988 to 2002. *Mol Genet Metab* 77: 304–313
- Blau N, Erlandsen H (2004) The metabolic and molecular bases of tetrahydrobiopterin-responsive phenylalanine hydroxylase deficiency. *Mol Genet Metab* 82: 101–111
- Fiege B, Ballhausen D, Kierat L, Leimbacher W, Goriouniv D, Schircks B, Thöny B, Blau N (2004) Plasma tetrahydrobiopterin and its pharmacokinetics following oral administration. *Mol Genet Metab* 81: 45–51
- Kure S, Hou DC, Ohura T, Iwamoto H, Suzuki S, Sugiyama N, Sakamoto O, Fujii K, Matsubara Y, Narisawa K (1999) Tetrahydrobiopterin-responsive phenylalanine hydroxylase deficiency. *J Pediatr* 135: 375–378
- Muntau AC, Roschinger W, Habich M, Demmelmair H, Hoffmann B, Sommerhoff CP, Roscher AA (2002) Tetrahydrobiopterin as an alternative treatment for mild phenylketonuria. *N Engl J Med* 347: 2122–2132
- Thöny B, Ding Z, Martinez A (2004) Tetrahydrobiopterin protects phenylalanine hydroxylase activity in vivo: implications for tetrahydrobiopterin-responsive hyperphenylalaninemia. *FEBS Lett* 577: 507–511