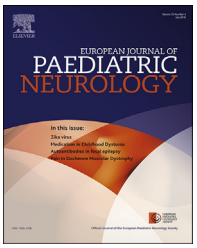
EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY XXX (2016) 1–4

Official Journal of the European Paediatric Neurology Society



Original article

Long-term safety and effectiveness of pramipexole in tetrahydrobiopterin deficiency

Francesco Porta[*], *Alberto Ponzone*, *Marco Spada*

Department of Pediatrics, University of Torino, Piazza Polonia 94, 10126, Torino, Italy

ARTICLE INFO

Article history:
Received 8 June 2016
Received in revised form
1 August 2016
Accepted 8 August 2016

Keywords:
BH_4 deficiency
Dopamine agonists
Pramipexole
Impulse control disorders

ABSTRACT

Tetrahydrobiopterin (BH_4) deficiencies are inherited neuro-metabolic disorders leading to monoamine neurotransmitters deficiency. An individualized replacement therapy with neurotransmitters precursors is necessary to restore dopaminergic and serotoninergic homeostasis. The correction of dopaminergic tone is complicated, like in Parkinson disease, by L-dopa short half-life and adverse effects. To improve this picture, since 2009 we introduced the non-ergot dopamine agonist pramipexole as an adjunct to L-dopa therapy in the treatment of the most common causes of BH_4 deficiency, 6-pyruvoyl tetrahydropterin synthase (PTPS) deficiency and dihydropteridine reductase (DHPR) deficiency. In the short-term period, this approach allowed substantial clinical advantages in affected patients, with amelioration and stabilization of the clinical picture on twice daily treatment administration and no adverse effect.

Here we describe the long-term clinical follow-up (83 ± 24 months) of seven patients with BH_4 deficiency treated with pramipexole. After a period of good clinical compensation (34 ± 1 months), different impulse control disorders (gambling, compulsive buying, and hypersexuality) were observed in three patients treated with high-dose pramipexole (0.030 −0.033 mg/kg/day) beyond adolescence. These psychiatric adverse effects promptly disappeared after curtailing pramipexole dose by 50–60%. Low-dose pramipexole therapy has been safe and effective in the long-term period in all treated patients (59 ± 9 months).

High-dose pramipexole therapy in BH_4 deficiency can be complicated, like in Parkinson disease, by psychiatric adverse effects. Low-dose pramipexole therapy (~0.010 mg/kg/day) has been safe and clinically effective on long-term follow-up, representing a helpful therapeutic option in patients with BH_4 deficiency.

1. Introduction

Tetrahydrobiopterin (BH_4) deficiencies are a heterogeneous group of rare inherited neuro-metabolic disorders characterized by monoamine neurotransmitters deficiency. Taken together, 6-pyruvoyl tetrahydropterin synthase deficiency (PTPS; MIM 261640) and dihydropteridine reductase deficiency (DHPR; MIM 261630) represent about 90% of all forms of BH_4 deficiency. Both conditions result in

* *Corresponding author*. Fax: +39 011 3135382.
E-mail addresses: porta.franc@gmail.com (F. Porta), fporta@unito.it (A. Ponzone), marco.spada@unito.it (M. Spada).
http://dx.doi.org/10.1016/j.ejpn.2016.08.006
1090-3798/

hyperphenylalaninemia and impaired catecholamine and serotonin neurotransmitter production. Clinical presentation occurs soon after birth or after some months, with neurological deterioration, developmental delay, seizures, truncal hypotonia and limb hypertonia, associated with parkinsonian features. Early diagnosis is facilitated by neonatal screening for hyperphenylalaninemia and prompt treatment essential for patients' outcome.[1–3] Standard therapy is very complex. The administration of synthetic BH_4 allows the correction of peripheral hyperphenylalaninemia, but scarce effects can be obtained at the central level. An individualized neurotransmitters replacement therapy is necessary to restore dopaminergic and serotoninergic homeostasis. The correction of dopaminergic neurotransmission represents the most critical aspect in BH_4 deficiency, mainly due to L-3,4 dihydroxyphenylalanine (L-dopa) short half-life and adverse effects. Three to six daily L-dopa administrations are generally necessary for a satisfactory clinical compensation, even if inhibitors of L-dopa catabolism, such as carbidopa, deprenyl and entacapone are concomitantly administered.[1] To improve this picture, in 2009 we introduced the non-ergot dopamine agonist pramipexole as an adjunct to L-dopa therapy in a series of patients with PTPS deficiency, and in 2012 in DHPR deficiency.[4,5] Here we provide the long-term safety and effectiveness of this implemented therapeutic regimen in BH_4 deficiency.

2. Patients and methods

Seven patients with BH_4 deficiency receiving pramipexole as an adjunct to L-dopa therapy were clinically followed for 83 ± 24 months. Their characteristics and actual dopaminergic regimens are reported in Table 1. Folinic acid supplementation was administered in patients with DHPR deficiency. Satisfactory control of peripheral hyperphenylalaninemia was obtained in all patients (mean blood phenylalanine 3.7 ± 1.8 mg/dl). Clinical visits were scheduled every 3–6 months on the basis of patients' age and therapeutic response. In all patients, full clinical evaluation was regularly accomplished also by applying an adapted Unified Parkinson's Disease Rating Scale (UPDRS). The occurrence of any side effect related to pramipexole therapy was systematically investigated.

3. Results

In all patients, all the previously described advantages of the implemented L-dopa + pramipexole therapy, including the amelioration and stabilization of the clinical picture on twice daily treatment administration, were maintained during the longitudinal clinical monitoring.[4,5] On long-term follow-up, no patients experienced any common side effect of pramipexole therapy, including dizziness, fainting, drowsiness, visual hallucinations, nausea, weakness, and constipation. After a variable period of good clinical compensation, however, older patients treated with high pramipexole dosage (0.030–0.033 mg/kg/day) experienced different psychiatric side effects (impulse control disorders) referable to pramipexole therapy. These adverse effects were invariably associated with

Table 1 – Characteristics and treatment of 7 patients affected by tetrahydropterin (BH_4) deficiency due to 6-pyruvoyl tetrahydropterin synthase (PTPS) or dihydropteridine reductase (DPPR) deficiency.

Patient	Age (years)	Mutant alleles	Follow-up on pramipexole therapy (months)	Dopaminergic treatment daily administrations	Current dopaminergic treatment					Other medications	
					Pramipexole (mg/kg/day)	L-dopa (mg/kg/day)	Carbidopa (mg/kg/day)	Selegiline (mg/kg/day)	Entacapone (mg/kg/day)	BH_4 (mg/kg/day)	OH-tryptophan (mg/kg/day)
		PTPS									
1	31	T76M/D136V	34	3	–	8.4	2.1	0.14	11.4	2.4	3.7
2	27	ΔV57/Δ(K29-32)	98	2	0.013	3.2	0.8	0.14	8.6	3.0	2.5
3	16	P87L/P87L	98	2	0.006	6.4	1.6	0.13	7.7	2.9	4.8
4	13	N52S/N52S	100	2	0.008	6.4	1.6	0.08	9.7	3.9	2.0
5	7	N52S/N52S	100	2	0.009	7.1	1.8	0.17	7.1	5.2	3.9
		DHPR									
6	24	G23D/Y150C	74	2	0.014	2.4	0.5	0.09	7.5	6.0	2.0
7	9	L14P/L14P	75	2	0.017	2.7	0.7	0.09	7.1	–	4.2

Please cite this article in press as: Porta F, et al., Long-term safety and effectiveness of pramipexole in tetrahydrobiopterin deficiency, European Journal of Paediatric Neurology (2016), http://dx.doi.org/10.1016/j.ejpn.2016.08.006