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LETTER TO THE EDITORS

Effects of dalfampridine on attacks in patients with episodic ataxia type 2: an observational study

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Dear Sirs,

Episodic ataxia type 2 (EA2) is the most frequent form of episodic ataxias and is caused in most patients by heterozygous mutations of the gene CACNA1A on chromosome 19p13. The clinical features of EA2 are recurrent attacks of ataxia, which can last from several hours to several days in association with interictal nystagmus (most often downbeat nystagmus) and other central ocular motor abnormalities [1, 2]. Today, treating EA2 involves use of two drugs [2, 3]. Firstly, the carbonic anhydrase inhibitor acetazolamide (ACT), which prevents attacks in 50–75 % of all EA2 patients (although so far, there are no placebo-controlled trials) [4, 5]; secondly, the potassium channel blocker 4-aminopyridine (4AP), which significantly reduces the frequency and duration of attacks and improves quality of life, as was shown in a randomized placebo-controlled cross-over study [6]. The sustained-release 4AP dalfampridine (Ampyra™ in the USA, Fampyra™ in the EU) was recently approved by the US Food and Drug Administration (January 2010) and the European Medicines Agency (July 2011) for the symptomatic treatment of gait disorders in multiple sclerosis [7, 8]. Based on the above mentioned study with the non-sustained release form of 4AP [6], we performed a prospective observational short-term proof-of-concept pilot study in which patients with genetically proven EA2 received 10 mg dalfampridine (Fampyra™) once a day for 6 days to evaluate its efficacy on the prevention of attacks in EA2.

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Two patients were included (for details see Table 1). Both patients had received 4AP (5 mg tid) in the past but they had not taken any drug specifically for EA2 for several months due to difficulties in availability of 4AP. After giving written consent, they received a standardized neurological examination and an electrocardiography was carried out before and 3 h after drug administration to measure the QTc-time. The patients took dalfampridine 10 mg once a day for 6 days. They were instructed to keep a diary to document the number of attacks and possible adverse effects. Follow-up interviews and examinations took place 1 week after the beginning of the treatment, and the second follow-up and examinations took place after the patients had stopped treatment for 1 week.

According to his diary, without medication the first patient typically experienced four to five attacks per week, while the second had attacks daily. Because the patients were known at our polyclinic for several years and because of the patients' self-report, we knew that the reported frequency of attacks without medication was representative without any fluctuations over a long-term period. Under medication no attacks occurred in both patients. Dalfampridine was well tolerated: none of the patients reported any adverse events. Further, no prolongation of the QTc-time was found or induced by dalfampridine. One week after treatment was stopped the first patient had four attacks per week and the second patient had attacks daily, i.e., the frequency of attacks was the same as before initiation of treatment.

In summary, this proof-of-concept observational study in two cases showed that the sustained release form of 4AP, dalfampridine, is able to prevent attacks in EA2 sufficiently even if our patients only received 10 mg once per day. The recommended dosage of dalfampridine for the treatment of gait disorder in multiple sclerosis is 10 mg twice per day [9]. Dalfampridine was tolerated well by both patients.

Table 1 Characteristics of both patients

	Age/sex	Mutation in the CACNA1A gene	Attacks 1[a]	Attacks 2[b]	Attacks 3[c]	QTc pre[d]	QTc post[e]	Oculomotor findings
1	47/m	p.R455X	4–5×/week	None	4×/week	397	406	Saccadic pursuit
2	33/m	A454T	Daily	None	Daily	410	409	Upbeat nystagmus, saccadic pursuit, horizontal gaze-evoked nystagmus

Frequency of attacks

[a] Before trial

[b] Under dalfampridine

[c] After 1-week wash-out

[d] QTc time in ms before administration of dalfampridine

[e] QTc time in ms 3 h after administration of dalfampridine

Based on animal studies in the tottering mouse, the presumed mode of action of 4AP is that it restores the precision of pacemaking in Purkinje cells [10]. The authors assume that this effect is even better achieved by a sustained release-form of 4AP because a constant level of the drug is evidently necessary to avoid a relapse of attacks [11]. Prospective placebo-controlled clinical trials are necessary to confirm these findings and to find the optimal dose.

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Conflicts of interest None.

Ethical standard Study has been performed in accordance with the Declaration of Helsinki and its later amendments.

References

1. Jen JC, Graves TD, Hess EJ et al (2007) Primary episodic ataxias: diagnosis, pathogenesis and treatment. Brain 130:2484–2493
2. Strupp M, Zwergal A, Brandt T (2007) Episodic ataxia type 2. Neurotherapeutics 4:267–273
3. Strupp M, Thurtell MJ, Shaikh AG, Brandt T, Zee DS, Leigh RJ (2011) Pharmacotherapy of vestibular and ocular motor disorders, including nystagmus. J Neurol 258:1207–1222
4. Harno H, Hirvonen T, Kaunisto MA et al (2004) Acetazolamide improves neurotological abnormalities in a family with episodic ataxia type 2 (EA-2). J Neurol 251:232–234
5. Griggs RC, Moxley RT 3rd, Lafrance RA, McQuillen J (1978) Hereditary paroxysmal ataxia: response to acetazolamide. Neurology 28:1259–1264
6. Strupp M, Kalla R, Claassen J et al (2011) A randomized trial of 4-aminopyridine in EA2 and related familial episodic ataxias. Neurology 77:269–275
7. Dalfampridine (Ampyra) for MS (2010) The medical letter on drugs and therapeutics 52:73–74
8. European Medicines Agency (2011). Available at: http://www.ema.europa.eu
9. FDA (2010). Available at: http://www.fda.gov
10. Alvina K, Khodakhah K (2010) The therapeutic mode of action of 4-aminopyridine in cerebellar ataxia. J Neurosci 30:7258–7268
11. Comunication in Neurology (www.neurology.org) on: Strupp M, Kalla R, Claassen J et al. (2011) A randomized trial of 4-aminopyridine in EA2 and related familial episodic ataxias. Neurology 77:269–275