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ORIGINAL COMMUNICATION

Dalfampridine in patients with downbeat nystagmus—an observational study

Jens Claassen · Katharina Feil · Stanislav Bardins · Julian Teufel · Rainer Spiegel · Roger Kalla · Erich Schneider · Klaus Jahn · Roman Schniepp · Michael Strupp

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Abstract We investigated the effects of dalfampridine, the sustained-release form of 4-aminopyridine, on slow phase velocity (SPV) and visual acuity (VA) in patients with downbeat nystagmus (DBN) and the side effects of the drug. In this proof-of-principle observational study, ten patients received dalfampridine 10 mg bid for 2 weeks. Recordings were conducted at baseline, 180 min after first administration, after 2 weeks of treatment and after 4 weeks of wash-out. Mean SPV decreased from a baseline of 2.12 deg/s ± 1.72 (mean ± SD) to 0.51 deg/s ± 1.00 180 min after first administration of dalfampridine 10 mg and to 0.89 deg/s ± 0.75 after 2 weeks of treatment with dalfampridine ($p < 0.05$; post hoc both: $p < 0.05$). After a wash-out period of 1 week, mean SPV increased to 2.30 deg/s ± 1.6 ($p < 0.05$; post hoc both: $p < 0.05$). The VA significantly improved during treatment with dalfampridine. Also, 50 % of patients did not report any side effects. The most common reported side effects were abdominal discomfort and dizziness. Dalfampridine is an effective treatment for DBN in terms of SPV. It was well-tolerated in all patients.

Keywords Clinical Neurology · Neuro-Ophthalmology · Neurotology · Downbeat nystagmus · Dalfampridine

Introduction

The most common form of persistent acquired nystagmus in the primary position is downbeat nystagmus (DBN), which is characterized by an upward drift followed by a fast correcting saccade in a downward direction [1]. Patients report oscillopsia, blurred vision and reduced VA as well as gait or stance difficulties [1]. There is increasing evidence that DBN is caused by an impaired function of cerebellar Purkinje cells (PC) [2–4] leading to a predominance of cells with downward on-direction [5] and an inhibition of superior vestibular nuclei neurons [3].

The 4-aminopyridine (4-AP) has already been used successfully in patients with DBN [6–9]. Animal studies

J. Claassen, K. Feil contributed equally to the article.

J. Claassen (✉) · K. Feil · S. Bardins · J. Teufel · R. Spiegel · R. Kalla · E. Schneider · K. Jahn · R. Schniepp · M. Strupp
Department of Neurology and German Center for Vertigo and Balance Disorders (IFBLMU), University of Munich Hospital, Munich, Germany
e-mail: jens.claassen@googlemail.com

K. Feil
e-mail: katharina.feil@med.uni-muenchen.de

S. Bardins
e-mail: sbardins@nefo.med.uni-muenchen.de

J. Teufel
e-mail: julian.teufel@med.uni-muenchen.de

R. Spiegel
e-mail: rainer_spiegel@hotmail.com

R. Kalla
e-mail: roger.kalla@med.uni-muenchen.de

E. Schneider
e-mail: erich.schneider@lrz.uni-muenchen.de

K. Jahn
e-mail: klaus.jahn@med.uni-muenchen.de

R. Schniepp
e-mail: roman.schniepp@med.uni-muenchen.de

M. Strupp
e-mail: michael.strupp@med.uni-muenchen.de

showed that 4-AP is able to increase the excitability of PC [10] and that, in a therapeutic dosage, it is able to restore the diminished precision of pacemaking in PC in an animal model of episodic ataxia type 2, the tottering mouse [11].

Dalfampridine, the sustained-release form of 4-AP, was approved for the symptomatic treatment of impaired gait in multiple sclerosis (FDA: 2010; EMA: 2011). It is thought that it might be even more effective than 4-AP because of a more constant blood concentration due to a different half-life time (4-AP: 3.5 h [12]; dalfampridine: 5.7–6.9 h [13]). Additionally, dalfampridine could be a potential treatment option because of less contraindication, such as a prolonged QTc-time which was shown to be a clinically relevant limitation for the use of 4-AP, and, thus, dalfampridine as an approved drug may provide a higher degree of reliability in terms of drug safety.

Based on these findings, we performed a proof-of-pharmaceutical-principle observational pilot study in ten patients with DBN to measure the effects of dalfampridine on SPV and VA in patients with DBN.

Methods

Patients

We treated ten patients (mean: 72.9 years; range: 59–87 years; four females; etiology: eight idiopathic, two cerebellar degeneration) with dalfampridine 10 mg bid for 2 weeks. Mean duration (± SD) of DBN was 4.4 ± 3.6 years. We defined "idiopathic" as downbeat nystagmus with or without additional cerebellar ocular motor signs but of unknown primary cause (in particular no stroke, hemorrhage, multiple sclerosis, or tumor). For clinical details see Table 1. All patients gave their informed consent.

Recording of eye movements

Measurements were carried out at baseline, 180 min after first administration and once at each further visit. Based on prior work [14], a 30-s eye movement recording at each position was carried out with 3-D video-oculography (EyeSeeCam© Resolution = 0.02°, Accuracy = 0.6°, Sampling rate = 120 Hz, Range ± 20° in horizontal and vertical direction). Patients were seated upright while recordings were done: 1) calibration primary position and 8.5° right, left, up and down, 2) gaze straight ahead with fixation at different positions (0°, 5°, 10°, 15°, 20°). Targets were video-projected at eye level onto a wall with white projector screen paint located 180 cm in front of the patient. The patient's head was fixated by a frame located on the right and the left of the head. The data-analysis of eye movements in the primary position (0°) was carried out off-line using Matlab 2007b (The Mathworks, Natick, MA, USA). The DBN in the other eye positions was measured as a pilot for further studies. Because of low data quality in the primary position in patient nine, data of eye movements at 20° right were used for data analysis. For further details see [14]. Responders were defined as patients with an improvement of SPV of more than 50 % between baseline and 180 min after first administration.

Table 1 Clinical characteristics of the patients with downbeat nystagmus, categorised by patient number, gender, age, neuro-ophthalmological findings, other neurological symptoms (Polyneuropathy = impaired ankle reflexes and/or pallhypaesthesia), magnetic resonance imaging (MRI) findings, etiology of downbeat nystagmus and duration of disease (in years) since onset of symptoms

Pat.	Sex/age	Etiology	Duration of disease	Brain-MRI findings	Neuro-ophthalmological findings (apart from DBN)	Polyneuropathy	BVP	Gait
1	F/87	Idiopathic	3	Normal	1, 2, 6, 7, incomplete OTR	No	No	Ataxia
2	F/77	Secondary	2	Cerebellar atrophy	1, 2, 5 (bilateral), 6, 7	Yes	Yes	Ataxia
3	M/80	Idiopathic	2	Normal	1, 2, 5 (bilateral), 6, 7	No	Yes	Normal
4	M/79	Idiopathic	12	Normal	1, 2, 3, 5 (bilateral), 6	Yes	No	Normal
5	M/71	Idiopathic	2	Normal	1, 2, 3, 5	No	No	Ataxia
6	M/72	Idiopathic	9	Normal	1, 2, 3, 6, 7, hypometric saccades downward	No	No	Ataxia
7	F/59	Idiopathic	5	Normal	1, 2, 3, 5, 6, SVV deviation	No	No	Normal
8	F/68	Idiopathic	1	Normal	1, 2, 3, 6, 7	No	No	Normal
9	M/71	Secondary (degeneration)	6	Cerebellar atrophy	1, 2, 3, 5, central positional nystagmus	Yes	No	Ataxia
10	M/65	Idiopathic	2	Unknown	1, 2, 5 (bilateral)	Yes	Yes	Ataxia

BVP bilateral vestibulopathy detected by caloric irrigation, *1* saccadic smooth pursuit, *2* gazed-evoked nystagmus, *3* provocation nystagmus, *4* rebound nystagmus, *5* pathological Head Thrust test developed by Halmagyi and Curthoys (uni- and/or bilateral), *6* impaired visual fixation suppression of the VOR, *7* pathological optokinetic reflex

Visual acuity and side effects

The VA was measured by a Snellen chart positioned at a distance of 6 meters at baseline, 180 min after first administration and once at each further visit. Side effects were documented by the patients during treatment.

Statistical data analysis

Data were not normally distributed; hence, non-parametric statistical tests were carried out (SPSS 20, IBM Corporation, Somers, NY, USA). To look for differences between baseline and the two measurements during medication on the one hand and between the two measurements during medication and the measurement after 4 weeks of wash-out on the other hand, a Friedman-test with χ^2-test-statistics was applied in each case. For individual post hoc comparisons, non-parametric Wilcoxon-test statistics with the Bonferroni correction were applied. In the eye-movement data, SPV of vertical eye movements was the dependent variable. DBN indicated by mean SPV (degrees/s) appears as a positive value, whereas the absence of DBN is a near zero value. The same statistical analysis was applied for VA as for SPV. The significance level was set at 5 %.

Results

In 180 min after the first administration of dalfampridine, the SPV decreased from a baseline of 2.12 deg/s ± 1.72 (mean ± SD) to 0.51 deg/s ± 1.00 and, after 2 weeks of treatment with dalfampridine, to 0.89 deg/s ± 0.75 (an example is shown in Fig. 1; for details see Table 2). There was an overall decrease of SPV from baseline (Friedman-test with χ^2-statistics = 15.2, $p < 0.001$, $N = 10$) with a significant post hoc difference between baseline and SPV 180 min after first administration ($p = 0.008$) and after 2 weeks of treatment ($p = 0.015$; see Fig. 2).

After a wash-out period of 4 weeks, mean SPV increased to 2.30 deg/s ± 1.6. There was an overall increase of SPV from both measurements during treatment (after 180 min, after 2 weeks) to the measurement after the 4-week wash-out (Friedman-test with χ^2-statistics = 8.3, $p < 0.016$, $N = 10$) with a significant post hoc difference between the SPV 180 min after first administration and the SPV after the wash-out ($p = 0.009$) and between the SPV after 2 weeks of treatment and the SPV after the wash-out ($p = 0.042$). It should be mentioned that four patients did not attend the last measurement for personal or logistical reasons. Note: In the other eye positions, results varied more from patient to patient with some of them also profiting from medication.

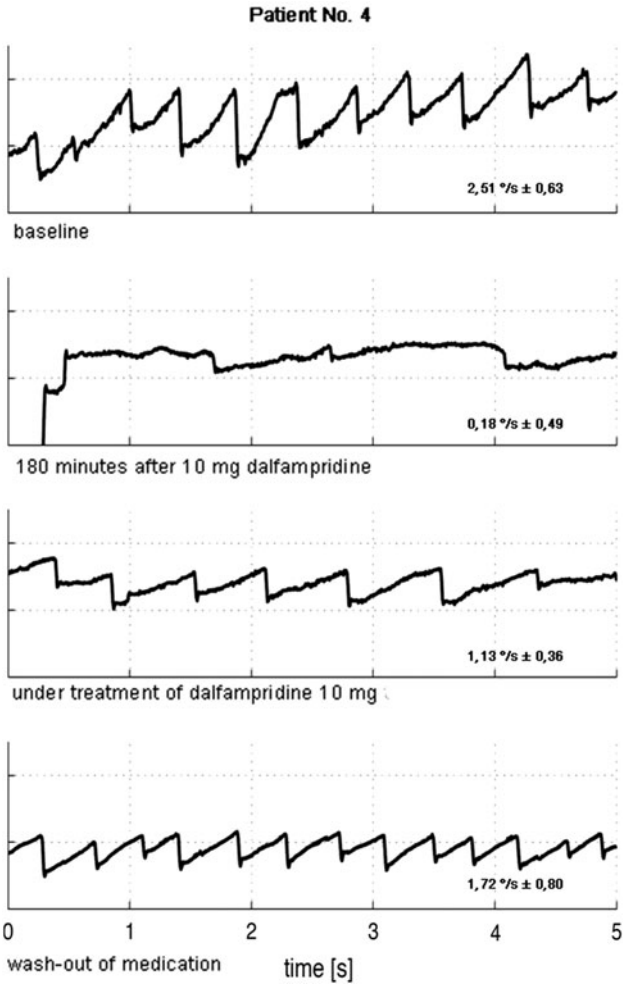

Fig. 1 Example of patient no. 4: Original recording of vertical eye position is shown at *baseline*, 180 min after first drug administration, after 2 weeks of drug administration and after 4 weeks of wash-out; values given are mean SPV in degrees/s (°/s)

Seventy percentage of the patients were responders to the medication after first administration; the rest of the patients initially only showed a marginal improvement of SPV. Two of the initial three non-responders further improved after 2 weeks on medication.

The VA increased from 0.72 ± 0.19 at baseline to 0.83 ± 0.21 180 min after first administration and 0.86 ± 0.21 after 2 weeks of treatment. There was an overall increase from baseline (Friedman-test with χ^2-statistics = 7.6, $p = 0.022$, $N = 10$) with a significant post hoc difference (180 min: 0.044; after 2 weeks: 0.027). There was no overall decrease from both measurements during treatment to the measurement after a 4-week wash-out ($p > 0.05$). This may be due to the fact that four patients did not attend the measurements. There was no significant correlation between SPV and VA ($p > 0.05$).

Table 2 Individual mean SPV in degree/s (°/s) and visual acuity (VA) of both eyes of each patient on different time spots and responder to medication

Pat.	Baseline		180 min after first administration of 10 mg dalfampridine		After 2 weeks of treatment with dalfampridine 10 mg bid		After wash-out of medication		Responder (≥50 % Δ SPV)
	SPV °/s ± SD	VA	SPV °/s ± SD	VA	SPV °/s ± SD	VA	SPV °/s ± SD	VA	
1	0.79 ± 0.74	0.80	−0.24 ± 0.38	0.80	0.73 ± 0.53	0.80	0.61 ± 0.65	0.55	Yes
2	1.71 ± 0.70	0.80	0.99 ± 1.36	1.00	0.78 ± 0.64	1.00	–	–	No
3	1.66 ± 0.68	0.58	0.50 ± 0.36	0.92	0.88 ± 0.50	1.00	1.06 ± 0.37	0.60	Yes
4	2.51 ± 0.63	0.65	0.18 ± 0.49	0.55	1.13 ± 0.36	0.70	1.72 ± 0.80	1.00	Yes
5	5.54 ± 1.00	1.00	0.49 ± 1.00	1.00	1.13 ± 1.00	1.00	3.29 ± 0.56	1.00	Yes
6	5.20 ± 0.70	0.60	2.53 ± 0.80	0.80	2.68 ± 0.90	1.00	4.99 ± 1.48	0.60	Yes
7	1.35 ± 0.38	0.72	1.13 ± 0.36	1.00	0.43 ± 0.82	1.00	2.06 ± 0.50	1.00	No
8	1.04 ± 0.60	1.00	−1.40 ± 0.67	1.00	−0.11 ± 0.36	1.00	–	–	Yes
9*	0.67 ± 0.43	0.63	0.23 ± 0.16	0.80	0.22 ± 1.10	0.70	–	–	Yes
10	1.65 ± 0.50	0.40	0.73 ± 0.40	0.40	0.93 ± 0.50	0.40	–	–	No

* SPV was measured at 20° eye position because of low data quality in primary position

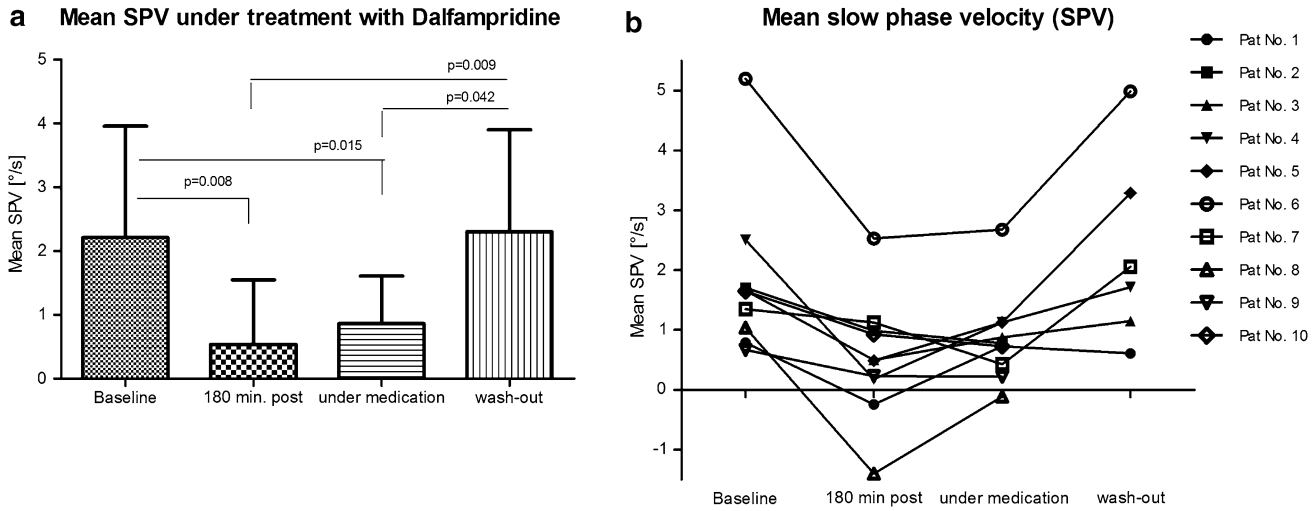

Fig. 2 **a** Mean SPV of all patients at baseline, 180 min after first drug administration, after 2 weeks of drug administration and after 4 weeks of wash-out. SPV was significantly lower under medication than at baseline or after the wash-out period (*left*). **b** Mean SPV of every patient at baseline, 180 min after first drug administration, after 2 weeks of drug administration and after 4 weeks of wash-out. Note: Data of SPV after wash-out is missing in four patients

Side effects were as follows: malaise (three patients), dizziness (two patients); five patients reported no side effects.

Discussion

In this observational proof-of-pharmacological-principle study for the sustained release form of 4-aminopyridine, we showed that dalfampridine significantly reduced SPV in patients with DBN. This effect started after first administration and lasted during continuous treatment with dalfampridine 10 mg bid. After treatment was stopped, SPV significantly increased to the level of baseline. The reduction of SPV after first administration was similar to previous studies with non-prolonged release aminopyridines in patients with DBN [6–9]. We further demonstrated that dalfampridine has a lasting positive effect and that without medication the intensity of DBN was as high as before treatment. The rate of response was higher (70 %) than in former studies with 4-AP (40 %) [7] and 3,4-diaminopyridine (59 %) [8] and increased even further to 90 % after 2 weeks on dalfampridine. The VA also improved significantly on dalfampridine. The improvement, however, did not significantly correlate with improvement of SPV of DBN, which suggests that

improvement of VA is of multifactorial origin. Dalfampridine was well tolerated. Initial dizziness and malaise could be minimized or even avoided by up-titrating treatment.

This study has considerable methodological shortcomings: first, it was only an observation. Second, it was neither blinded nor placebo-controlled. The parameters used, however, were either measured objectively or could be quantified. Third, the number of patients was quite low. Therefore, of course, a prospective, randomized, placebo-controlled and well-powered study is necessary.

In conclusion, dalfampridine is a well-tolerated effective drug that reduces SPV of DBN and improves VA.

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

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