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Early effect of dalfampridine in patients with MS: A multi-instrumental approach to better investigate responsiveness

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ABSTRACT

Background: 4-aminopyridine (4-AP) is a potassium-channel blocker able to enhance walking speed in MS improving the action potentials of demyelinated axons on which internodal potassium channels are exposed.
Objective: to study early 4-AP effect with clinical, subjective, neurophysiological and neuroradiological tools.
Methods: Clinical (Timed 25-Foot Walk - T25FW, Timed Up-And-Go - TUG), subjective (MS Walking Scale-12 - MSWS-12), neurophysiological (Motor Evoked Potentials - MEPs) and imaging (Diffusion Tensor Imaging - DTI) evaluations were performed before (T0) and after (T1) 14 days of 4-AP treatment. MEPs were recorded from Abductor Hallucis of both legs. A Tract-Based-Spatial-Statistics (TBSS) was performed on DTI.
Results: We found a significant difference between T0 and T1 for T25FW, TUG, MSWS-12 ($p \leq 0.001$) in the whole patients' sample (23 subjects, median EDSS 6.0) and decrease of Central Motor Conduction Time and increase of mean Amplitude (Amp) at T1 ($p = 0.008$ and $p = 0.006$). We also recorded a significant difference of T25FW, TUG, MSWS-12 and Amp in clinical responder (CR) patients (CR: amelioration >20% at T25FW). TBSS showed a significant Mean and Radial Diffusivity reduction in the corticospinal tracts ($p < 0.05$) of the whole group of patients; this reduction was also found in the CR subgroup.
Conclusion: Neurophysiological and neuroradiological parameters were modified in MS patients treated with 4-AP, and most of them reported a subjective improvement of their motor performances after treatment. The use of clinical, subjective, neurophysiological and neuroradiological tools could help to better explore MS patients responsiveness to 4-AP.

1. Introduction

Walking impairment is a common complaint in patients affected by Multiple Sclerosis (MS), with direct effects on independence, quality of life, activities of daily living and costs. A recent review reported that 75% of persons with MS (PWMS) in population based studies experienced mobility problems. Walking impairment is present at the early stages of the disease and it is considered crucial for body functioning in MS patients' perspective [11,22].

Recently, a dalfampridine extended-release (4-AP) formulation was approved for treatment of ambulation deficits in MS patients. The mechanisms underlying the therapeutic effects are still unclear: in this regard, 4-AP may block the juxtaparanodal K^+ channels exposed on demyelinated axons, increasing amplitude and duration of the action potential. Moreover, 4-AP may increase neurotransmitter release and the number of synaptic terminals activated by an action potential, thus potentiating synaptic transmission, and ultimately enhancing skeletal muscle twitch tension [31].

Goodman demonstrated improvement in walking speed after treatment with 4-AP, evaluated by means of the Timed-25 Foot Walk Test (T25FW) [9]. A recent systematic review about symptomatic treatment of MS with 4-AP or its sustained-release formulation (SR-AP) reported a clinically significant improvement in walking speed after treatment (approximately 25% increase) in about 40% patients [16].

Most of the studies on the effect of 4-AP demonstrated not only a clinical but also a self-reported improvement in patients' walking speed [7–10]. Ruck et al. demonstrated a sustained effect on walking impairment from the clinical and subjective point of view, persisting after 9–12 months [28].

As widely reported, clinical response was observed only in a proportion of patients treated [9,10] and no clear explanation to such heterogeneity has been found yet.

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Study results demonstrated the potential role of neurophysiological measures in the preliminary evaluation and early identification of PWMS who may benefit from treatment with 4-AP. However, only a few studies combined the use of clinical and neurophysiological evaluations [6,20,28,37] and, to our knowledge, only one study explored the efficacy of 4-AP in PWMS using neuroimaging methods [20].

Among all the advanced MR techniques, Diffusion Tensor Imaging (DTI) proved to be a reliable tool to detect microstructural alterations in the white matter [15]. To date, no studies are yet available on the potential relationship between clinical improvement in walking speed and changes in DTI parameters after assumption of 4-AP in PWMS.

We believe that the combined use of clinical, subjective, neurophysiological and neuroradiological evaluations might provide a more detailed understanding of 4-AP mechanism of action, improving the identification of MS patients eligible for treatment. Hence, we report the first study investigating the early effect of 4-AP in PWMS, by means of clinical, subjective, neurophysiological, and DTI evaluations.

2. Materials and methods

This longitudinal explorative study was conducted at the Neurological Institute Foundation C. Besta between February and November 2013. Patients with relapsing-remittent (RR), secondary progressive (SP) and primary progressive (PP) MS, according to the revised Mc Donald criteria 2010, were invited to participate [25]. The following inclusion criteria were considered: a) Expanded Disability Status Scale (EDSS) score between 4.0 and 7.0 [19]; b) no relapse and steroid treatment in the 30 days before the first evaluation; c) absence of contraindications to Motor Evoked Potentials (MEPs) and magnetic resonance imaging (MRI) evaluations. The protocol was approved by the local Ethics Committee. All participants included provided written informed consent. The treatment period lasted 14 days; 4-AP dose was 10 mg b.i.d.

Patients underwent a clinical, neurophysiological and radiological evaluation at T0 (the day before starting the treatment) and at T1 (the last day the drug was taken, day 14). All the adverse events were recorded during the treatment period.

2.1. Clinical evaluation

An expert neurologist performed the neurological evaluation and assigned the EDSS score to each subject. The following assessments were carried out at both time-points: 1) Timed 25-Foot Walk (T25FW) according to the instructions for the Multiple Sclerosis Functional Composite [24]; 2) Timed Up-An-Go Test (TUG) [23]; the amount of time taken to perform tests 1) and 2) was recorded; lower times correspond to better motor performances; 3) the Multiple Sclerosis Walking Scale-12 (MSWS-12) [13], a self-reported measure of the impact of MS on the individual's walking ability composed of 12 items, each scored 1–5; scores of the 12 items are summed to transform to a 0–100 scale; lower scores correspond to better motor performances. Patients were also asked to complete the abbreviated Treatment Satisfaction Questionnaire for Medication (TSQM-9) at T1 [1]. The TSQM-9 is a questionnaire designed to assess patients' satisfaction with medication providing scores on three factors – Effectiveness, Convenience and Global Satisfaction; higher scores mean higher satisfaction.

We used clinical and subjective criteria of responsiveness to the treatment. According to Hobart, patients were classified as clinical responders (CR) when T25FW improved of at least 20% from T0 to T1 [14]. Moreover, as recently proposed, we used the decrease of 6.9 points of the MSWS-12 score to identify patients subjectively reporting improvement after treatment (subjective responders - SR) [12].

2.2. Neurophysiological evaluation

MEPs were elicited by Transcranial Magnetic Stimulation (TMS), using a MagVenture MagOption (Medtronic, Skovlunde, Denmark) stimulator with circular coil, in accordance with standard protocols applied on MS [18,28]. The TMS-induced MEPs were recorded using surface electrodes placed on the muscle Abductor Hallucis (AH) of the two legs. The coil was placed over the vertex for the stimulation of the legs' motor cortical areas and pulses were delivered with a biphasic current; for pre-activation of AH, patients were asked to perform a brief, weak voluntary muscle contraction (about 20% of maximum force). Six consecutive MEPs were collected with the stimulator output adjusted to 80–100% maximum output to elicit the best MEP responses [6]. The Central Motor Conduction Time (CMCT) was calculated as the difference between the shortest latency of MEPs obtained from cortical and lumbar roots stimulation. The mean peak-to-peak amplitude (AMP) of cortical MEPs was calculated for each leg as the average amplitude of the MEPs obtained. For the subsequent analysis, the means of the individual right and left CMCTs and amplitudes were determined as a global measure of pyramidal involvement, as suggested by Zeller et al. [37]. AT both time points, the same stimulation intensity was used and CMCT and amplitude have been determined in a blinded fashion.

Patients from whom TMS after stimulation was not obtained have been excluded from the analysis.

2.3. Radiological evaluation

All the exams were performed on a 1.5T Siemens Magnetom Avanto Unit (Siemens; Erlangen, Germany) using a 8-channel head coil. The MRI protocol consisted of the following sequences: 1) Axial double-echo (TR = 3210 ms, TE = 10/94 ms, FOV = 256 × 224 mm, voxel-size = 0.89 × 0.89 × 3 mm); 2) Sagittal inversion-recovery volumetric (TR = 4000 ms, TE = 365 ms, TI = 400 ms, FA = 120°, FOV = 256 × 256 mm, voxel-size = 1 × 1 × 1 mm); 3) Coronal Fluid attenuated inversion recovery (FLAIR) volumetric (TR = 5000 ms, TE = 469 ms, TI = 1800 ms, FA = 120°, FOV = 256 × 256 mm, voxel size = 1 × 1 × 1 mm); 4) Axial single-shot echo-planar spin-echo DTI (TR = 9200 ms, TE = 100 ms, FOV = 128 × 128 mm, voxel-size = 2.2 × 2.2 × 2.2 mm) with a b factor of 1200 s/mm^2, 64 non-collinear DWI directions and one b = 0 s/mm^2 volume every 8 DWI volumes.

DTI raw volumes were processed to correct for motion artefacts and eddy-current non-linear distortions using the FMRIB's Diffusion Toolbox (FDT), part of the FSL's software library (FSL 5.0.4, http://www.fmrib.ox.ac.uk/fsl). After the pre-processing step, tensor was fitted voxel-by-voxel using DTI fit in order to estimate the main DTI metrics: Fractional Anisotropy (FA), Mean Diffusivity (MD), Axial Diffusivity (AD) and Radial Diffusivity (RD) maps were calculated for each subject. FA represents the degree of water diffusion directionality and ranges between 0 and 1, i.e. minimum and maximum anisotropy; MD reflects the entity of water diffusion in any direction; AD measures the degree of diffusivity in the main axonal direction and it has been shown to be sensitive to axonal damage/degeneration [2,32,34,35]; RD represents the entity of the transverse diffusivity and is related to the degree of myelination [2,32–35] and [36]. Increases of MD and RD are usually associated with loss of myelin, whereas a decrease in AD is associated to axonal loss. FA values are highest in compact WM tracts [29].

The Tract-Based Spatial Statistics (TBSS) analysis was conducted following a validated procedure described elsewhere [30]. Mean skeletal diffusional values were calculated for each subject and for each diffusional metric.

Patients with imaging artefacts that precluded TBSS analysis have been excluded.

The number of lesions on FLAIR/T2 and T1 weighted images had been evaluated for each patient before and after drug administration