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Fampridine treatment and walking distance in multiple sclerosis: A randomised controlled trial

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HIGHLIGHTS

- The present study assessed the effects of modified-release fampridine on walking distance in MS.
- Fampridine treatment has potential benefits for improved walking distance in MS.
- Nerve excitability techniques may be of use in selecting MS patients who will respond to fampridine.

ABSTRACT

Objective: To explore the benefits of modified-release fampridine on walking distance in MS.
Methods: This was a randomised double-blind, placebo-controlled crossover trial of fampridine in 25 MS patients. The primary outcome measure was the six minute walk test (6MWT). A p-value < 10% led to rejection of the null hypothesis.
Results: The pre-specified criterion for statistical significance was met, with a 17 m improvement in 6MWT in the treatment arm. In addition, baseline S2 accommodation, a nerve excitability parameter that reflects slow K^+ channel activity, modified the effect of fampridine. For patients who had abnormally high S2 accommodation values, there was a 28 m improvement in the 6MWT ($p = 0.04$). In contrast, for patients with low S2 values, a 0 m improvement was noted ($p = 1.0$).
Conclusion: The study provides evidence that fampridine may improve walking distance. Nerve excitability assessment may be useful in selecting those patients who are most likely to gain benefit from fampridine.
Significance: Fampridine may improve walking distance in MS. Nerve excitability assessment may assist in identifying those patients most likely to respond to fampridine.

1. Introduction

Modified-release fampridine is a slow release form of 4-aminopyridine that has been approved worldwide for the treatment of multiple sclerosis-related walking disability. Recent phase II and phase III studies of fampridine have demonstrated sustained clinical benefits on walking speed over short distances of 25 feet in ~40% of MS patients (Goodman et al., 2008, 2009, 2010). Unlike the short-release form of 4-aminopyridine which has significant adverse effects, including the development of seizures, fampridine has a more acceptable safety profile with a lower risk of serious adverse events in controlled trials (Goodman et al., 2009). The neurological effects of fampridine have been attributed to blockade of voltage-gated K^+ channels in demyelinated axons and potentiation of neurotransmitter release in central and peripheral nervous systems (Krishnan and Kiernan, 2013).

While the effects of fampridine on walking over short distances have been clearly established, the potential benefit over longer walking distances has not been evaluated. This remains an important clinical question given that walking disability is a highly

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prevalent complication of MS, affecting ~75% of patients (Lerdal et al., 2007; Nogueira et al., 2013). A number of different physiological mechanisms have been implicated in the development of motor disability in MS, including impaired cerebral neurotransmitter release (Perretti et al., 2004), increased levels of proinflammatory cytokines (Heesen et al., 2006) and axonal dysfunction leading to conduction failure in demyelinated axons (Bostock et al., 1978; Sherratt et al., 1980).

Animal studies have demonstrated that 4-aminopyridine may improve conduction in demyelinated axons by blocking voltage-gated K^+ channels and thereby increasing the amplitude and duration of the action potential (Sherratt et al., 1980). The present pilot study had two major objectives. The first was to explore the potential activity of fampridine on walking distance in MS patients in a cohort of unselected MS patients. The second was to evaluate the potential effects of fampridine on ion channel properties in MS patients, using nerve excitability techniques (Krishnan et al., 2009), a clinical method that provides information regarding axonal ion channel function in human peripheral nerves. This technique has recently been studied as a potential surrogate marker for the assessment of ion channel dysfunction in central nervous system disorders including epilepsy, spinal cord injury, episodic ataxia and MS (Kiernan et al., 2005; Lin et al., 2007; Ng et al., 2008; Tomlinson et al., 2010). This study was therefore also designed to investigate whether excitability techniques may have a role in identifying those patients most likely to benefit from fampridine treatment.

2. Patients and methods

2.1. Study design

This was a randomised double-blind, placebo-controlled crossover trial of fampridine (10 mg twice daily) in subjects with both relapsing and progressive forms of MS. The study was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN 12611000799954). Patients were recruited consecutively from August 2011 from the Multiple Sclerosis Clinic at Prince of Wales Hospital in Sydney, Australia. Assessments were undertaken in the Institute of Neurological Sciences, Prince of Wales Hospital in Sydney, Australia with the last assessment completed in October 2013. The study was approved by institutional ethics committees for research in human subjects. Written informed consent was obtained from all participants.

2.2. Subjects

Eligible subjects were 18–80 years of age and had a diagnosis of multiple sclerosis, according to the 2010 McDonald criteria (Polman et al., 2011). Of the 25 subjects assessed, 13 patients (52%) had relapsing-remitting MS, 7 had secondary progressive MS (28%) and 4 had primary progressive MS (16%). Exclusion criteria reflected the known contraindications to fampridine including history of seizures, current pregnancy, and moderate-severe renal impairment. In addition, patients were excluded if they had a history of relapses in the 60 days prior to enrolment or an Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) score of >6.0, due to the potential difficulties with completing the outcomes measures.

2.3. Randomisation and treatment protocol

Patients were randomised using a permuted blocks method in a 1:1 ratio to fampridine 10 mg b.d. or placebo for three months (period 1). At the end of three months, all patients entered a four-week washout period, before receiving the alternate treatment for a further 3 months (period 2). The NHMRC Clinical Trials Centre, University of Sydney generated the randomisation lists for the Prince of Wales Hospital Pharmacy. Patients were then assigned to the interventions sequentially, i.e. a participant was assigned to the next intervention in the random sequence. Fampridine 10 mg tablets or matched placebo tablets were packaged in identical bottles, and stored in Prince of Wales Hospital Pharmacy. Bottles containing either active fampridine tablets or matched placebo tablets were identifiable only to Pharmacy staff authorised to work on the study, and they were also unblinded to treatment assignments. Assessments were performed at baseline (i.e. prior to commencement of the study drug) and at monthly intervals for the duration of the study.

2.4. Outcome measures

The primary outcome measure was the six-minute walk test (6MWT), a measurement that has been previously validated for the assessment of ambulation in MS patients (Goldman et al., 2008). Nerve excitability measures, a clinical method that provides information on ion channel function in peripheral nerve axons (Krishnan et al., 2009), was assessed as a secondary outcome measure. Excitability studies were performed using previously described threshold tracking protocols applied to the median nerve at the wrist (Kiernan et al., 2000), with the compound muscle action potential (CMAP) recorded from abductor pollicis brevis using surface electrodes (Unomedical, Bikerod, Denmark). Patients were screened for clinical or neurophysiological evidence of carpal tunnel syndrome, prior to excitability testing. Skin temperature was monitored at the site of stimulation and was maintained at >32 °C. QTRAC automated software (Digitimer, London, UK) was used to apply the TRONDNF protocol and excitability measures were obtained in five testing paradigms, including: stimulus response curves, strength-duration properties (a marker of persistent Na^+ currents), depolarizing and hyperpolarizing threshold electrotonus (a measure of internodal ion channel function), current-threshold relationship (a measure of the rectifying properties of the nerve) and a recovery cycle (an assessment of the activity of nodal transient Na^+ channels and nodal and juxtaparanodal K^+ channels of slow and fast kinetics).

To obtain stimulus–response curves, 1 ms duration currents of increasing intensity were applied until the maximal CMAP response was established. For the remainder of the protocol, a target of ~40% maximum CMAP was set and the stimulus required to achieve this target was termed "threshold". Strength-duration-time-constant was established as the relationship between strength and duration of a stimulus using four stimulus durations (0.2, 0.4, 0.8 and 1 ms). Threshold electrotonus curves were obtained by recording the percentage of threshold change when 1 ms test pulses were applied during and after 100 ms subthreshold conditioning currents of +40% (depolarizing – TEd) and −40% (hyperpolarizing – TEh) control threshold. TE provides information on internodal properties and overall axonal membrane potential. Current threshold relationship was determined by mapping the change in threshold when 1 ms test impulses were delivered following 200 ms depolarizing and hyperpolarizing conditioning currents (+50 to −100 ms). This provides information regarding rectifying properties of the axon. A recovery cycle was recorded by assessing the change in threshold that occurs over 200 ms following supramaximal stimulation.

The other secondary outcome measures included Handgrip dynamometry, to assess maximum grip strength, Timed 25-foot walk test (Goodman et al., 2009), Nine-hole pegboard test, as a measure of upper limb motor function, Medical Research Council manual muscle test (MRC), assessed separately for upper and