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REVIEW

Sustained-release fampridine in Multiple Sclerosis

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Abstract
Sustained-release fampridine, a slow release formulation of 4-aminopyridine, is a voltage-dependent potassium channel blocker licensed for the treatment of walking difficulties in multiple sclerosis (MS). Studies have demonstrated that approximately one-third of MS patients respond with a clear benefit to their walking speed.
Sustained-release Fampridine is not currently available on the National Health Service (NHS), although it has been approved by the Food and Drug Administration (FDA) in the USA and European Medicine Agency (EMA). It appears to have an acceptable adverse event profile, with data from open-label extension studies now becoming available. Concerns have been raised that the use of fampridine may increase the risk of seizures, which were seen at higher rates in patients treated with high doses of sustained-release fampridine. The rate of seizures in those patients on lower doses has not been found to be significantly increased. There are significant barriers at present to the widespread use of fampridine in the UK, which have limited its use in clinical practice to date. Patients with MS are in need of interventions to improve walking and many clinicians feel that this drug may have a role in the symptomatic management of MS.

Contents

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1. Introduction

Multiple Sclerosis (MS) is a complex disorder of the central nervous system (CNS), the cause of which is unknown. It is characterized by progressive demyelination and axonal degeneration within the CNS. MS is a disease of young people, particularly women, with an average age of onset of 25–30 years. It is estimated that there are currently 100–120 people per 100,000 living with MS in England and Wales (NICE, 2012).

MS leads to a variety of symptoms including walking impairment, which is one of the most disabling features. Up to 75% of MS patients suffer from clinically significant walking disturbance (Heesen et al., 2008; Hobart et al., 2001; Swingler and Compston, 1992); 50% of MS patients require assistance with walking 20 years after their first symptom (Coles, 2009). During a normal gait cycle an individual is supported by a single leg 80% of the time with bilateral support during 20% of the gait cycle (Cuccurullo, 2012). In people with MS, the proportion of time spent with bilateral support is greater and therefore the speed of walking is slower (Remelius et al., 2012).

Walking impairment in MS is complex and multifactorial. Factors affecting walking in MS include weakness and spasticity of the lower extremities, sensory impairment and fatigue. Walking disability has a high impact on the personal, professional and social burden of the disease (Phan-Ba et al., 2012). There are many drugs used in the symptomatic management of MS, but until recently none were licensed for the specific treatment of walking impairment.

2. Role of 4-aminopyridine

The neurophysiology underlying the possible mechanism (s) of action of 4-aminopyridine (4-AP) is discussed in the accompanying article (Baker, in press). There has been increasing interest in the use of 4-AP as a therapeutic intervention to improve walking in MS.

A randomised, double-blind, placebo-controlled study conducted by Bever et al. (Bever et al., 1994), focused on the pharmacokinetics of immediate-release 4-AP, together with the degree of clinical improvement and the adverse effects experienced by MS patients. It was demonstrated that clinical improvement was related to total 4-AP exposure, and adverse events to peak serum levels. 4-AP has a narrow therapeutic window; so to improve safety, limit the peak-dose side effects including seizures and acute encephalopathy (Murray and Newsom-Davis, 1981), and to generate prolonged adequate serum levels, the sustained-release K_v channel blocker, sustained-release (SR) fampridine, was developed.

3. Efficacy and trial evidence for sustained-release fampridine

There have been previous studies examining the therapeutic use of 4-AP, but this article focuses on sustained-release 4-AP, SR-fampridine. Trial evidence for the use of SR-fampridine is summarised in Table 1.

The first pilot double-blind placebo-controlled, crossover study of SR-fampridine of 10 MS patients with stable motor deficits (Expanded Disability Status Scale, EDSS 6.0–7.5) was in 1997 (Schwid et al., 1997). There was a wide range of walking impairment in this relatively small proof-of-concept trial, which nonetheless managed to reach statistical significance. 9 out of 10 patients in the treatment group demonstrated an objective improvement in speed of walking compared to placebo based on a timed test ($p=0.02$), and 7 felt subjectively better.

A randomised, double-blind, placebo-controlled, parallel-group trial of SR-fampridine in 25 MS patients was published in 2007 (Goodman et al., 2007). This trial, performed in 2000–2001, was a dose-escalation trial focussing on both dose-related efficacy and safety. The primary analysis, the change from baseline in the timed 25-foot walk (T25FW), did not achieve statistical significance. However, post-hoc analysis demonstrated a significant improvement in walking speed (in feet/second) in the SR-fampridine group ($p=0.$ å03). Convulsions were seen in 2 patients receiving high dose (>25 mg twice-daily) SR-fampridine.

The efficacy and dose response characteristics of SR-fampridine were explored in a phase II multicentre, randomised, placebo-controlled, parallel trial with 206 participants – MS-F202 (Goodman et al., 2008). Patients were randomised 1:1:1:1 to placebo, SR-fampridine 10 mg twice daily, 15 mg twice daily and 20 mg twice daily. The primary outcome measure was the percentage change from baseline in average walking speed measured by the T25FW. The proportion of patients demonstrating a >20% improvement in walking speed did not reach statistical significance between any of the doses of SR-fampridine and placebo (SR-fampridine 10 mg, 23.5%; 15 mg, 26.0%; 20 mg, 15.8%; vs. placebo, 12.8%). In a post-hoc analysis, 36.7% patients treated with SR-fampridine demonstrated a consistent improvement in the T25FW versus 8.5% of the placebo group. The sub-group of the SR-fampridine group demonstrating a consistent improvement in walking speed was designated a "responder" group. There was a consistent mean improvement of 25–29% in walking speed for fampridine-treated responders over the double-blind treatment period. The use of the T25FW as a marker of treatment response was thought to be validated by the fact that the responder group also demonstrated improvements in the self-assessed measure of ambulation, the 12-item multiple sclerosis walking scale (MSWS-12). There was also a non-significant trend towards an improvement in the clinician global impression (CGI) scores in the responder group ($p=0.056$). Treatment discontinuations secondary to adverse effects such as seizures, chest discomfort and balance disorders were more commonly seen in the higher dose treatment groups (≥15 mg).

Post-hoc analysis of the above study, demonstrated that patients who met a responder criterion for a consistent response (increase in walking speed in ≥3 visits on drug