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REVIEW

Enhancing Neural Transmission in Multiple Sclerosis (4-Aminopyridine Therapy)

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Abstract Enhancing neural transmission by improving axonal conduction and synaptic neurotransmitter release is a novel strategy to improve symptoms in multiple sclerosis. Dalfampridine (4-aminopyridine extended-release) is a first-in-class medication that targets the damaged nervous system through blockage of voltage-gated potassium channels. Through a series of clinical trials, dalfampridine (dosed at 10 mg twice daily) has been found to improve walking speed by approximately 25 % on average in one third of individuals with multiple sclerosis regardless of disease stage. Furthermore, it significantly improves patients' perception of their ambulatory disability and may improve lower extremity strength. Given the mechanism of action, the most serious adverse effect is its proconvulsant property, which occurs more frequently at high serum concentrations. The most common adverse events include increased falls, urinary tract infections, dizziness, insomnia, and headaches. Despite these potential side-effects, the vast majority of individuals who derive benefit continue on the treatment. The exact mechanism of action is uncertain, as is the reason for response variability. The medication serves as proof-of-concept that targeting axonal transmission can improve disability in multiple sclerosis.

Keywords Multiple sclerosis · Gait disorder · Potassium channel · Neural transmission · Dalfampridine

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Introduction

Multiple sclerosis (MS) is the most common disease of the central nervous system in young adults leading to sustained disability. A wide variety of deficits contribute to disability, including visual disturbances, weakness, ataxia, and gait dysfunction, fatigue, bladder and bowel difficulties, and cognitive dysfunction. The disease involves immune-mediated destruction of the central nervous system myelin, as well as a variable amount of direct axonal injury. Although the underlying mechanism of disability progression remains uncertain, inflammatory demyelination is likely a significant contributor, as it leads to slowed conduction velocity along affected axons. Current disease-modifying therapies target the heightened immune response, but do not directly target the damaged nervous system.

Dalfampridine (4-aminopyridine extended-release; termed fampridine sustained-release in pre-2010 literature and outside the United States) is a novel therapy that directly targets demyelinated axons presumably by improving conduction and facilitating synaptic transmission. 4-aminopyridine (4-AP) is a broad-spectrum antagonist of voltage-gated potassium (Kv) channels [1, 2]. The compound has been previously studied for spinal cord injury, neuromuscular junction disorders, and Alzheimer's disease [3, 4]. A related compound 3,4 diaminopyridine has also been studied in MS, as well as neuromuscular disease, most notably Lambert-Eaton syndrome [5].

Primarily based on 2 phase 3 randomized, placebo-controlled clinical trials, dalfampridine has been shown to improve walking speed on the timed 25-foot walk (T25FW) test by approximately 25 % on average in one third of subjects [6, 7] Gait dysfunction is 1 of the leading causes of physical disability among patients with MS. Recently diagnosed patients with relapsing-remitting MS can have reduced walking speed and stride length, as well as balance impairment, suggesting that the process leading to gait

dysfunction frequently begins early in the disease [8]. Overall, approximately 75 % of MS patients struggle with mobility problems leading to loss of independence, physical appearance of disability, and unemployment [9]. As such, gait dysfunction contributes significantly to reduced quality of life [10, 11]. Thus, improving mobility through enhanced neural transmission, in addition to targeting inflammatory demyelination, can lead to enhancement of quality of life for MS patients.

Mechanism of Action

Demyelination of central axons leads to exposure of the paranodal and juxtaparanodal regions (areas immediately adjacent to the nodes of Ranvier). These axonal regions are rich in Kv channels. It is theorized that exposure of these channels in demyelinated axons contributes significantly to dysfunction of action potential propagation as it causes the cell to move closer to voltage equilibrium for potassium [1]. In addition, exposure of slow Kv channels impairs axonal generation of repetitive impulses by interfering with hyperpolarization [12]. 4-AP also increases presynaptic transmission by increasing end-terminal influx of calcium [13]. This may be due to the indirect effect of Kv blockage on calcium influx or direct effects of 4-AP on voltage-gated calcium channels, thereby increasing cytoplasmic free calcium [14–16].

Remyelination of damaged axons depends on proliferation of oligodendrocytes. The oligodendrocytes originate from oligodentrocyte precursor cells (OPC), and thus OPC proliferation is likely to be important in recovery from relapses. There is evidence that certain Kv channel subtypes play a role in OPC proliferation, and thus blockage could hypothetically help facilitate remyelination [17, 18]. 4-AP could also have an immunomodulatory role as immune cells (e.g., T and B cells, microglia, and macrophages) also express Kv channels. Furthermore, the number of Kv channels is significantly upregulated when these cells are activated and seem to play a role in activation and proliferation [14, 19, 20].

Pharmacology and Pharmacokinetics

The Kv channel has 4 alpha subunits, each containing 6 membrane-spanning, alpha-helical regions. The subunits form pores that are either homotetramers or heterotetramers [1]. 4-AP is a broad-spectrum Kv channel-blocking agent that has the greatest affinity for slowly inactivating channels. It is part of a family of monoamino and diamino pyridine derivatives, where there is an amino substitution in the fourth position of the pyridine ring [1, 12]. 4-AP is a small, lipid soluble, and readily crosses the blood brain barrier. 4-AP binds to the Kv channel from the cytoplasmic side at the opening of the pore, thus occluding it [1].

Early studies of 4-AP showed an increase in action potential duration and amplitude when measured on experimentally demyelinated mammalian peripheral nerve fibers [21, 22]. Small human clinical trials using intravenous and orally administered immediate-release formulations of 4-AP were subsequently completed in MS and spinal cord injury [23–28]. Pharmacologic trials have shown that immediate-release 4-AP has a mean time to maximum concentration of 1 h and a mean half-life of 3.5 h. The maximum observed plasma concentration for the 10 mg and 25 mg doses were 46.4 and >100 ng/mL, respectively. The peak serum concentration was clearly dose related and followed a linear distribution [2]. The medication is primarily excreted renally with a total urinary excretion of 99 % after 24 h. It has negligible protein binding and limited conversion to metabolites [29, 30].

Immediate-release formulations of 4-AP were found to have a narrow therapeutic window, with higher concentrations acting as a proconvulsant [31]. This finding, along with the need for frequent dosing throughout the day, motivated creation of an extended-release formulation (initially entitled sustained-release). This extended-release formulation has a mean time to maximum concentration of 3.2 to 5 h and a mean half-life of 5.2 to 6.4 h. The maximum observed plasma concentration for the 10 mg dose was 22 ng/mL (50 % lower than the immediate release formulation) [29, 30]. Thus, the sustained-release formulation had lower peak concentrations, and could be dosed less frequently. It is important to note, that in the setting of moderate-to-severe renal impairment (i.e., creatinine clearance, <40 mL/min), peak plasma concentration was 1.5 to 2 times higher with time to maximum concentration of 6 to 8 h and a half-life of 8 to 14 h [29].

Clinical Trials

For the last 30 years, small safety and efficacy trials of 4-AP were completed in MS patients. Initial studies showed improvement in visual performance, motor function, coordination, gait, and oculomotor function. No serious adverse effects were identified in these early studies [32, 33]. In 1994, Bever et al. [34] published a randomized, placebo-controlled trial testing the immediate-release formulation of 4-AP (fampridine). The trial documented an improvement in visual contrast-sensitivity and strength, but did not find a significant difference in Expanded Disability Status Scale scores. Serum concentrations >60 ng/mL were associated with a higher incidence of adverse events. One subject had a generalized tonic-clonic seizure at a concentration of

104 ng/mL, and another had an acute confusional episode at 114 ng/mL.

Schwid et al. [35] published a small, double blind, placebo-controlled crossover study of dalfampridine (4-AP sustained release) in 1997 that helped identify walking speed as an outcome of interest. They used a dose of 17.5 mg twice daily for 1 week. The study found improvement in timed gait and nonsignificant improvement in timed stair climbing, grip strength, or Expanded Disability Status Scale. Importantly, no serious adverse events were documented. In 2007 and 2008, Goodman et al. [36, 37] published 2 randomized, double-blind, placebo-controlled dose trials of dalfampridine; the first trial assessed the safety and efficacy of dose escalation, and the second trial compared parallel groups of 3 doses. The latter trial found an increase in baseline lower extremity strength in the 3-drug treatment groups, but found that serious adverse events were more common in the higher-dosed groups. In the initial study, 2 subjects had convulsions at 30 to 35 mg twice daily dosing. In the latter study, 2 subjects experienced seizures, and 1 had encephalopathy in the 20 mg group.

These preliminary studies informed the design of the first phase 3, randomized, controlled, double-blind clinical trial [6]. This study evaluated dalfampridine (10 mg twice daily dosing) for 14 weeks *versus* a placebo in 301 subjects. The mean peak dalfampridine concentration was 27.6 ng/mL. In the dalfampridine group, there were 35 % of subjects *versus* 8 % in the placebo group who were deemed "timed walk responders." Responders were defined as patients who had a faster walking speed on the T25FW for at least 3 of 4 visits during the double-blind treatment period compared with their maximum speed for any of the 5 off-drug visits. Mean improvement of walking speed in responders was 25 % *versus* 5 % in the placebo group. This improvement was maintained during the 14-week treatment period. This study also used the 12-item MS walking scale, which evaluates a subject's perception of their ambulatory disability (with a lower score correlating with a lower perceived disability). The change in score had significantly improved in the responder group (-6.84 *vs* 0.05 in the nonresponders). This was an important observation as it supported the conclusion that the improvement in walking speed to be not only statistically, but also clinically, relevant [6]. A recent report evaluated what change in the T25FW would statistically be considered "minimally important," and found the estimate to be around 20 % [38]. The trial also assessed clinical global impression scores as well as lower extremity strength, which were significantly improved in responders [6].

Goodman et al. [7] published the results of the second phase 3 trial in 2010. The study evaluated dalfampridine 10 mg twice daily dosing for 9 weeks versus placebo in 239 subjects. The mean peak dalfampridine concentration was 28.5-30.2 ng/mL. 43 % of subjects in the dalfampridine group were found to be treatment responders (*vs* 9 % in the placebo group). Improvement in walking speed in responders was 25 % in the treatment group *versus* 8 % in the placebo group. Again, the responder group showed significant improvement in the 12-item MS walking scale score (-6.04 *vs* 0.85), and improvement in a measure of lower extremity strength [7]. Table 1 summarizes the efficacy data from the 2 phase 3 trials.

Table 1 Summary of Efficacy Measures in 2 Pivotal, Phase III Clinical Trials

Efficacy measure	Goodman, et al. (2009) [6]	Goodman, et al. (2010) [7]
T25FW responders (*vs* placebo)	35 % (8 %)	42.9 % (9.3 %)
Average change in walking speed in responders (*vs* placebo)	25.2 % (4.7 %)	24.7 % (7.7 %)
Average change in MSWS-12 score (*vs* placebo)	-6.84 (0.05)	-6.04 (0.85)
Average change in LEMMT score (*vs* placebo)	0.18 (0.04)	0.145 (0.042)

LEMMT = Lower Extremity Manual Muscle Test [6, 7]; MSWS-12= 12-Item Multiple Sclerosis Walking Scale; T25FW test = timed 25-foot walk test

All differences shown were significant with p value<0.05

Safety

The most severe adverse events identified by trials have been seizures and acute encephalopathy. These seem to occur with high serum concentrations of the medication (>100 ng/mL), and were more common with the immediate-release formulation [4]. The theorized mechanism for its proconvulsant effect is increased neuronal excitability from potassium channel blockade. When estimating the increased seizure risk

Table 2 Most Frequent Adverse Events Recorded in 2 Pivotal, Phase III Clinical Trials*

Most Frequent AEs	Goodman, et al. (2009) [6]	Goodman, et al. (2010) [7]
Urinary tract infection	14 %	17.5 %
Fall	16 %	11.7 %
Insomnia	8 %	10 %
Headache	6 %	9.2 %
Dizziness	8 %	8.3 %
Nausea	6 %	8.3 %
Asthenia	6 %	8.3 %
Upper respiratory infection	6 %	5.8 %
Back pain	6 %	5.8 %
Balance disorder	6 %	5.8 %

*[6, 7]

associated with the medication, 1 must account for the overall increased incidence of seizures in the MS population (2 % *vs* 1 % in the general population) [39]. In an initial study by Bever et al. [34] on immediate-release 4-AP, 1 patient had a generalized-tonic clonic seizure with a serum concentration of 104 ng/mL [4]. In the dalfampridine dose ranging trials by Goodman [36], 2 patients had seizures in each study on doses ranging from 20 to 35 mg [36, 37]. In the phase 3 pivotal trials, only 1 seizure occurred in the initial study, but it was associated with sepsis secondary to community-acquired pneumonia [6]. There have been reports of toxicity related to pharmacies independently compounding an immediate-release formulation of the medication. A concern is that these preparations may not always meet uniformity requirements [31]. Overall, it seems that when the extended-release preparation is used at the appropriate dosage (10 mg twice daily), the incidence of seizures is no higher than that of the MS population as a whole. However, given the risk for seizures at higher serum concentrations, the medication should be avoided in those with a history of seizures or renal dysfunction.

Other serious adverse events occurring on treatment (although not clearly related to the medication) have been severe anxiety, sepsis (secondary to community-acquired pneumonia), cellulitis, pyelonephritis, patellar fracture, coronary artery disease, and cholelithiasis. The most common adverse effects are summarized in Table 2, and these include increased frequency of falls, urinary tract infections, insomnia, dizziness, and headache. Less frequently encountered adverse effects have included fatigue, nausea, upper respiratory infections, asthenia, back pain, balance dysfunction, arthralgia, and paresthesias [6, 7]. There is no indication that the medication increases the incidence of MS relapses. There is no indication of cardiotoxicity at standard doses, although there are reports of cardiac arrhythmias in patients taking unregulated formulations [31]. Data from open-label extension studies show no new long-term safety concerns and 73 % continued usage as of 2008 [40].

As previously described, the medication is excreted via the kidneys, and thus patients with moderate-to-severe renal insufficiency have 1.5 to 2 times higher peak serum concentrations [29]. Caution should be used in patients with mild renal impairment (creatinine clearance, 51-80 mL/min), but no specific dose adjustment is recommended. The medication should be avoided in patients with moderate-to-severe renal impairment (creatinine clearance, <51 mL/min).

Conclusion and Future Directions

Dalfampridine is a unique treatment that is believed to work by improving axonal conduction and facilitating synaptic transmission. It significantly increases walking speed in approximately one third of individuals, which can help improve independence, employment opportunity, and ultimately quality of life. Seizure is the adverse event of most concern, but when used at standard dosing, the incidence is not likely higher than that of the general MS population.

It is unclear why some patients (30-40 %) are treatment responders and others are not. It has been proposed that lesion location may influence response to treatment. Responders may have demyelinated axons more relevant to gait, and thus they are more likely to have benefit from treatment. However, the subjects included in each pivotal trial had T25FW for >8 seconds, and so it is likely that the majority of patients had demyelinating lesions relevant to ambulation. The discrepancy could involve individual polymorphisms of voltage-gated potassium channels rendering specific channels more or less susceptible to the medication. Future studies to evaluate the cause of the discrepancy may allow identification of potential responders.

Dalfampridine serves as proof-of-concept that targeting the damaged nervous system can improve symptoms. Alternate mechanisms for enhancing axonal conduction should be sought. If treatments are developed with such varied mechanisms, significant symptomatic improvement could potentially be achieved through combination therapies.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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