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REVIEW

Dalfampridine: Review of its Efficacy in Improving Gait in Patients with Multiple Sclerosis

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Abstract: Multiple sclerosis (MS) is a progressive immune-mediated neurodegenerative disease of human central nervous system (CNS), which causes irreversible disability in young adults. The cause and cure for MS remain unknown. Pathophysiology of MS includes two arms: inflammatory demyelination and neurodegeneration. The inflammatory demyelination of MS which is mainly promoted by a massive activation of the immune system against putative CNS antigen(s) leads to loss of oligodendrocyte/myelin complex which slows down or halts impulse conduction in denuded axons. Practically, loss of myelin significantly reduces signal conduction along the demyelinated axons through alterations in the distribution of axonal ion channels. Dalfampridine (4-aminopyridine or 4-AP) is an oral potassium channel blocker, which was recently approved by FDA for symptomatic treatment of MS. Dalfampridine, which acts at the central and peripheral nervous systems, enhances conduction in demyelinated axons and improves walking ability of MS patients. A number of clinical trials have evaluated the safety and efficacy of fampridine in MS patients with the degree of gait improvement as the main outcome. The objective of this manuscript is to provide an overview of the pharmacology, pharmacokinetics, clinical trials, side effects and interactions of dalfampridine used in treatment of MS patients.

Keywords: dalfampridine, multiple sclerosis, gait, 4-AP

Introduction

Multiple sclerosis (MS) is a chronic progressive inflammatory and neurodegenerative disease of human central nervous system (CNS) which usually affects young adults, with a reported median age of onset of approximately 30 years.[1] In approximately 85% of patients with MS, the disease is initially recognized by a relapsing-remitting course which may eventually lead to a progressive deterioration of neurological status along with significant loss of neurological function.[2] Neuropathologically, MS presents with various patterns, however, inflammatory demyelination and oligodendrocyte loss and neuronal and axonal degeneration[3] constitute salient features of microscopic examination of MS lesions. Currently, the cause and cure for MS remain elusive and in many cases MS ends with significant neurological disabilities. While massive activation of the inflammatory arm of the immune system against putative CNS antigen(s) such as myelin basis protein plays a major role in the pathogenesis of the demyelinating process of MS, the neurodegenerative process prevails in the long run and causes significant cognitive and functional deterioration in affected patients.

Electrophysiologic examination of demyelinated lesions indicates conduction block as the predominant feature of these lesions. The pathophysiologic basis of such conduction block in MS rests on segmental demyelination with loss of whole internodes of myelin. In normal individuals, blocking the voltage-gated potassium channels does not have any significant impact on conduction of the action potential since these channels are enclosed by layers of myelin sheath. However, loss of myelin during pathogenesis of MS, exposes the potassium channels and interferes with production and conduction of the action potential. In fact, the impulse conduction fails specifically at the site of demyelination, while the normal segments of the axons on both sides continue their impulse conduction normally. Certain features which determine the impulse conduction block in demyelinated axon consist of the size of demyelinated area, extent of myelin loss along the internode, and the time elapsed since demyelination happened. The duration of demyelination is an important factor since myelin loss sets a number of adaptive axonal responses in motion. For example,

development of a revised group of ion channels along the demyelinated membrane may result in restoration of impulse conduction. The size of the demyelinated lesion is another significant factor since axons repair centripetally inside the lesion and extensive lengths of demyelination are repaired slowly which in turn reflects the fact that the chance of functional recovery correlated inversely with the lesion size. Loss of myelin sheath is another significant factor in the process of conduction block. It appears that myelin loss involving the paranodal area is stronger factor in blocking conduction than a comparable loss of distributed along the internode.

Apart from the segmental demyelination which is associated with conduction block, histopathologic examination of MS tissue has shown that some node are inappropriately wide in MS lesions due to paranodal demyelination or retraction of the paranodes.[4]

Another salient feature of demyelinated axons is abnormal reorganization of the ion channels. The speedy conduction velocity and uninterrupted transmission of electric signals in mammalian myelinated axons rest on the appropriate spatial distribution ofion-selective channels. Na+ channels are gathered at nodes of Ranvier in concentrations which are ~25 times that of internodal regions.[5] These clusters are essential for efflux of ion currents at nodes and allow fast saltatory conduction. On the contrary, other studies have demonstrated that K+ currents appear only after loosening of the myelin sheath from the axonal membrane.[6] K+ channels are located only in paranodal and internodal areas and normally they do not contribute to generation of the action potential.[7] Scientific studies which have focused on action potential propagation in normal and demyelinated axons have revealed a reorganization of axolemmal ion channels, which in turn leads to conduction impairments. Loss or decrease of sodium channels from the nodes of Ranvier[8] causes the nodes to be inexcitable and leads to conduction block. Sherratt et al[9] demonstrated that in demyelinated regions sodium channel concentrations are reduced, while voltage-sensitive potassium channels (which are not active on normal myelinated axons) become detectable. This exposure of K channels at juxtaparanodal region leads to efflux through fast K channels and causes axonal conduction block by preventing sufficient depolarization and initiation

of the action potential at the node of Ranvier.[10] Demyelination also exposes slow K channels, further interrupting normal hyperpolarization and blunting normal repetitive impulse release from the presynaptic area terminals.[11] In 1981, Bostock et al[12] demonstrated that potassium channel blockers dendrotoxin and 4-aminopyridine improved conduction impairments in experimentally demyelinated axons and laid the scientific rationale for clinical studies of potassium channel blockers in MS patients.

Dalfampridine: Introduction and Mechanism of Action

Fampridine (or 4-Aminopyridine [4-AP]) is a broad-spectrum blocker of voltage-sensitive potassium channels, which has been demonstrated to improve conduction and propagation of the action potential along the demyelinated axons. In addition, fampridine increases the duration of the pre-synaptic action potential and amplitude which in turn leads to increased transmitter release.[13] Apart from being a voltage-activated potassium channel blocker, 4-aminopyridine potentiates synaptic and neuro-muscular transmission by affecting the beta subunit of voltage-activated calcium channels.[14] This novel mode of action of 4-aminopyridine which occurs independent from its blocking effect on the potassium channels, provides another rationale for its positive effect on the neuromuscular function in patients with spinal cord injury, myasthenia gravis and MS.

Pharmacokinetics

Dalfampridine (4-aminopyridine) (marketed as Ampyra™ by Accorda Therapeutics, Inc., Hawthorne, NY, USA) is one of the three isomeric amines of pyridine with chemical formula $H_2NC_5H_4N$, which acts a selective potassium-channel blocker. Dalfampridine, which is a sustained-release oral form of fampridine, is rapidly and completely absorbed from the gastrointestinal tract, however, its absolute bioavailability has not been determined. Compared to an aqueous oral solution, the extended release tablet shows a relative bioavailability of 96%, with a delayed absorption pattern which provides a less rapid rise to a lower maximum plasma concentration. In healthy volunteers who took a single 10 mg dose of dalfampridine, peak serum concentrations were reached 3 to 4 hours following oral administration and it was almost completely and rapidly eliminated by urinary excretion. Elimination of dalfampridine and its metabolites are almost complete after 24 hours. The elimination half-life of dalfampridine is 6.4 hours in healthy individuals. As a lipid-soluble agent, dalfampridine passes through the blood brain barrier and blocks potassium channels in both the central and peripheral nervous systems.[15] Daldampridine binds reversibly to the cytoplasmic side of potassium channels, blocking the ion conductance pathway which in turn prolongs the action potentials in unmyelinated nerve fibers and enhances neurotransmitter release at synaptic endings.[16] Dalfampridine has been studied extensively in symptomatic treatment of MS patients with walking impairment. Impairment of ambulation is a major neurological deficit in MS patients and significantly interferes with their quality of life. It is hypothesized that dalfampridine improves clinical symptoms of MS by restoring conduction in demyelinated axons through voltage-dependent potassium channel blockade.[15] In addition, dalfampridine has been used for treatment of Lambert-Eaton myasthenic syndrome,[17] where it prolongs neurotransmitter release at the neuromuscular junction. Studies involving animal models have demonstrated that can reverse tetrodotoxin toxicity.[18]

Pharmacokinetic assessmentsof both immediate-release and sustained release formulations of fampridine have been done in normal individuals as well as those patients with MS and spinal cord damage. Uges et al[19] performed a pharmacokinetic study involving 9 healthy individuals (7 men and 2 women) to assess immediate-release fampridine in intravenous, entric-coated, and uncoated oral formulations. The bioavailability of the enteric coated tablets was calculated from the area under the serum concentration curve 95% ± 29% (mean ± SD), which was not much different from that calculated from urinary excretion 98% ± 8%. There was no evidence that metabolism of fampridine involved glucoronidation, sulfonation, or N-acetylation. Investigators reported that 89.6% ± 7.5% of the medication was excreted in the urine unchanged after 24 hours of the intravenous formulation and 86.1% ± 2.7% with the entric coated formulation. The pharmacokinetics of the sustained-release fampridine has been studied in MS patients. One dose-ranging pharmacokinetic study included

12 MS patients who received increasing doses of sustained-release fampridine from 7.5 to 25 mg every 12 hours.[20] The investigators reported a mean time to peak concentration of 5 hours and mean serum half-life of 5.2 hours.

Vollmer et al[21] studied the pharmacokinetics of dalfampridine in clinical trials of MS patients and found that multiple dosing of this medication was associated with its accumulation. In addition, the investigators noted that the steady-state pharmacokinetic profile of fampridine sustained-release 20 mg BID administered for 2 weeks appeared to support the administration of twice-daily dosing in this population. This dosage was generally well tolerated by study participants.

Dosage, Formulation, and Administration

Dalfampridine (Ampyra) is available as 10 mg extended release tablets with relative bioavailability of 96%, peak of plasma concentration of 3–4 hours and half life of 5.2–6.5 hours.

Clinical trials of Dalfampridine in Multiple Sclerosis

The major goals of treating MS patients consist of prevention of exacerbations, limiting disability progression, and improving cognitive decline. The available treatments for MS fall under two categories: disease modifying agents such as Beta-interferons and glatiramer acetate and medications for symptomatic treatment such as baclofen for treatment of spasticity and dalfampridine which is used to restore the impulse conduction along the demyelinated axons and improve muscle strength and walking ability.

In January 2010, dalfampridine was approved by the FDA for symptomatic treatment of MS patients with specific indication for improving walking. In the past 4-aminopyridine has been used as an experimental agent which presumably enhances nerve conduction of demyelinated axons through its effects on potassium channels for treatment of fatigue in MS. Sheean et al[22] reported that use of fampridine in MS patients was associated with improvements in fatigue as well motor and visual symptoms. In addition, dalfampridine has been assessed and studied in other cohorts of MS patients in the context of various clinical trials to determine its efficacy in improving

MS patients' ambulation. In this manuscript only some of the more significant clinical trials have been cited and discussed.

Using quantitative measures of motor function, Schwid et al[23] performed one of the earlier clinical trials of sustained-release fampridine-SR in MS patients. This was a randomized, double-blind, placebo-controlled, crossover clinical trial included 10 patients with clinically definite MS, limb weakness and stable motor deficits (EDSS 6.0–7.5). Study subjects were randomized to be treated with sustain-release fampridine 17.5 mg orally twice daily for a period of one week or placebo for a period of one week. There was a one-week period of washout between prior to crossover. Study outcomes included time to walk 8 meters, time to climb four stairs, maximum voluntary isometric contraction measured quiantitatively, manual muscle testing, grip strength, EDSS, and the patient's global impression. Of these outcomes, only timed gait progressed on sustain-release fampridine compared with placebo in 9 of the study participants. Seven participants preferred the medication over placebo based on the findings from the patient's global impression. This clinical trial did not reveal any significant side effects.

In 2002, Goodman et al[24] reported the results of a four-center randomized, double-blind placebo-controlled study of controlled release aminopyridine in 31 MS patients. The study participants were treated with increasing doses of 20 to 80 mg of aminopyridine daily in divided doses. A total of 25 participants received the active medication and 11 participants were treated with placebo. Outcome measures of this clinical trial consisted of timed ambulation, manual testing of leg strength, paced auditory serial addition task, 9-hole peg test, and a fatigue diary. The results of this clinical trial indicated a statistically significant and dose-related enhancement of timed ambulation in AP-treated patients compared to those who received placebo. A significant enhancement of leg strength was also observed in approximately 11% of AP-treated participants compared with a 4% worsening of placebo-treated participants, $P = 0.01$. The reported side effects consisted of dizziness, insomnia, paresthesia, nausea, headache, tremor, pain and anxiety. On daily doses of 60 and 70 mg two MS patients seized. A phase 2, multi-center, randomized,

double-blind, placebo-controlled, parallel-group, dose-comparison (10, 15, or 20 mg twice daily orally) clinical trial of sustained-release fampridine in MS patients demonstrated significantly more consistent responders as determined by improvement in ambulation as compared to the placebo-group: 36.7% versus 8.5%.[25] Fampridine was generally well tolerated and serious and severe adverse effects were more common in those patients who received the highest dose.

A multi-center randomized, double-blinded, placebo-controlled phase 2 dose-raning clinical trial was conducted by Goodman et al which assessed the concept that whether the dose of fampridine-SR could be safely elevated to 80 mg/daily in patients with MS.[26] A cohort of 36 MS patients were randomized in a 2 to 1 ratio to be treated with an increasing dose of fampridine-SR for a period of 8 weeks. The dosage of fampridine-SR was escalated from 10 to 40 mg twice daily by increments of 5 mg twice daily on a weekly schedule. A group of evaluations were done once a week which included MS Functional Composite (MSFC), fatigue questionnaires, and lower extremity manual muscle testing. The objectives of this clinical trial included assessment of the safety of higher doses of fampridine-SR as well as the efficacy and dose-response to this drug by MS patients. Five study participants were terminated from fampridine-SR due to adverse events at doses larger than 25 mg and these events consisted of seizures in two individuals at doses of 30 and 35 mg twice daily. No subjects in the placebo arm of the study dropped out due to the adverse events. In the group which was treated with fampridine-SR compared to the group which was treated with placebo showed improvement in the lower extremity muscle strength (prospective analysis) and walking speed (post-hoc analysis). No significant differences were noticed in other MSFC measure or fatigue scores. The investigators concluded that future clinical trials should restrict the dose of fampridine-SR to 20 mg twice daily and walking speed and lower extremity muscle strength tests are potential efficacy measurements. Another phase 3 multicenter clinical trial of dafampridine which was controlled and double-blind included 301 MS patients of different types (27% with relapsing-remitting MS and 73% with progressive MS). During the 14 weeks duration of this trial, participants were assigned in a ratio of 3 to 1 to be treated with dalfampridine 10 mg (N = 229) or placebo (N = 72) orally twice daily for a period of 14 weeks.[27] The primary aim of this study included steady progress on timed 25-foot walk to define responses with proportion of timed walk responders in each arm. The investigators reported a higher proportion of timed walk responders in the fampridine-treated arm (78/224 or 35%) compared to those who were treated with placebo (6/72 or 8%). The therapeutic effect of fampridine continued during the treatment phase. There were no new safety findings in this study. Based on the results of this study, treatment of MS patients with fampridine was associated with gait improvement with a decrease in patient's gait impairment.

A more recent executed phase 3 multi-center double-blind clinical trial of extended-release dalfampridine in patients with definite MS of any clinical course assessed the efficacy, safety, and pharmacodynamics of extended release oral dalfampridine in these patients.[28] The length of this study was 9 weeks and the participants were randomized to be treated with dalfampridine (10 mg twice daily; n = 120) or placebo (n = 119) for a period of 9 weeks. The primary aim of this study consisted of constant progress on the Timed 25-Foot Walk, with percentage of time walk responders (TWRs) in each treatment arm. The last on-treatment assessment collected information from 8 to 12 hours postdose, to assess and determine the persistence of the impact of the medication. The results of this clinical trial indicated that the quantity of TWRs was higher in the dalfampridine-treated group (51/119 or 42.9%) compared to the placebo-treated group (11/118 or 9.3%. $P < 0.0001$). The average enhancement of walking speed among the dalfampridine-treated TWRs during the 8-week efficacy assessment period was 24.7% compared to baseline; the mean enhancement during the finalon-treatment visit was 25.7%, reflecting continuation of the impact of medication over the interdosing phase. The investigators did not find any new safety concerns. The authors concluded that this clinical trial generated class 1 evidence that treatment of patients with definite MS with extended-release dalfampridinetablets caused meaningful enhancement of walking ability in and the effect of the medication continued persisted between doses.

Side Effects, Interactions, and Contraindications

Based on the animal studies, dalfampridine demonstrates properties of a powerful convulsant stemming from its broad-spectrum suppressing activity on the potassium channels in the peripheral and central nervous systems.[11] Based on a number of clinical trials of 4-AP side effects consist of dizziness, insomnia, paresthesia, nausea of mild to moderate intensity, tremor, pain, anxiety and seizures.[29–34]

Dalfampridine is neither a substrate for nor an inhibitor of the P-glycoprotein transporter, therefore its pharmacokinetics is not affected by the medications which suppress this transporter. It does not interact with the medications which are substrates for the P-glycoprotein transporter. In addition, it has no interactions with beta-interferons.

Dalfampridine is contraindicated in patients with history of epilepsy or history of severe renal insufficiency.[35] The reason that dalfampridine use is not recommended in epileptic patients is that epilepsy is characterized by abnormal neuronal depolarization with excessive inhibition on potassium channels, hence a further reduction of potassium channel activity by dalfampridine is not advised.

Conclusion

Pathogenesis of MS involves loss of oligodendrocyte/ myelin complex which turn results in re-organization of axolemmal ion channels which leads to conduction abnormalities including conduction delay or block. Pharmacological agents which block potassium channels have been investigated in the context of clinical trials with positive impact on impulse conduction in experimentally-induced demyelination as well as in patients with MS. Dalfampridine (which is marketed as Ampyra), is an extended release form of fampridine (4-aminopyridine), which has been recently approved by the US FDA for symptomatic treatment of MS patients. While this new oral blocker of voltage-gated potassium channels does not have any impact on the underlying pathology of MS, it has been demonstrated to improve fatigue and walking ability in these patients.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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