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Dalfampridine: Review Analysis on Multiple Sclerosis and Parkinson's disease related to Waking Disability

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Abstract

The Multiple sclerosis and Parkinson's disease are neurodegenerative disease which effect on the central nervous system. Which loss the coordination between brain and body multiple sclerosis is the progressive, autoimmune disease. It occurs when your immune system attack myelin cell in your brain and spinal cord. Parkinson's disease is caused by the loss of dopamine in a part of your brain called substantial nigra, which causes and cure are unknown. MS disease are commonly occurs in young adult i.e. 20to 40 years where as Parkinson's disease commonly occurs in old persons i.e. 60 years. Both the disease do not occur in same person, both disease loss the coordination of brain and body related to gait dysfunction. Dalfampridine is one of the available treatments for to improve the walking in MS and Parkinson's disease related to gait dysfunction. Dalfampridine is the oral potassium channel blocker which was recently approved by FDA for sympathomimetic treatment in MS. Dalfampridine which acts on central and peripheral nervous system enhances conduction in demyelinated axon and improves waking ability of MS patient.

Keywords: Multiple sclerosis; Parkinson's disease; Gait; Dalfampridine

Introduction

Multiple sclerosis and Parkinson's disease are neurodegenerative disease which affect on the central nervous system, which loss the coordination between brain and body. Multiple sclerosis is progressive, autoimmune and diabolizing disorder which affect the central nervous system specially brain, spinal cord and nerve fiber. Which causes and cure are unknown it causes irreversible disability in young adult. It characterized by inflammation, demyelization and degenerative changes. In the case of MS massive activation of the immune system against putative CNS leads to loss of myelin complex which shows slow down the complex of impulse conduction in denuded axon [1]. Most of the people diagnosed of MS are between the age of 20 to 40 years old and the number of are affected 2 to 3 times more than number of men. By means of 50 to 30 per 1000000 people MS affect about 2.3 million people globally [2]. In the US 2500,000 to 350,000 for the multiple sclerosis and 50 percent patient will need to walking within 15 years after onset of the disease [3]. MS is the chronic disorder of body immune system that affect the central nervous system, normally nerve fiber carry electrical impulses from the spinal cord providing communication between brain, arms and leg. The person suffering from multiple sclerosis which result in muscle weakness, loss of vision, loss of coordination, problem with gait and movement, fatigue, cogitative deficit, increased neuropathy discrepancies, paralysis and decreased ability of thinking or remember [1,2]. Treatment of the MS is unknown it also affected 3 to 5 percent in children under the age of 16 [4]. Electrophsioliogic test of demyelinated injury indicate conduction block as a predominant feature of this injury. The pathophysiologic basis of conduction in MS loss of entire myelin internodes. On the other hand loss of myelin in MS exposes the potassium channel and interferes with generation and conduction of action potential. In fact the impulse conduction fails specially transmission normally [5-7].

Parkinson's disease (PD) is chronic progressive neurodegenerative disorder that early characterized by death of predominately dopamine-producing neurons in a specific area of the brain called substantial nigra. Dopamine is a neurotransmitter that is primarily responsible for controlling movement, emotional responses and the capability to feel delight and pain [8]. The cells that make dopamine are impaired and as the disease progresses, the more dopamine-producing brain cells die. Once a person develops motor symptoms, the amount of dopamine loss is already substantial. The brain ultimately reaches a point where it stops producing dopamine in any essential amount, thus increasing problems with movement. First describe by Gemes Parkinson's in an essay entailed an essay on the shaking placy in 1817 [9]. PD is characterized by the cardial feature of rest tremor bradykinins, rigidity and postural instability, loss of balance, effect on body movement and a variety of motor and non-motor symptoms, with aging and increasing global life span of the global population [10]. PD is a paralysis agent which typically develops between the age of 55 and 65 years. This disease organized two classification; genetic and sporadic, genetic pd fallows Medellin inheritance. Somatic PD which account for about 90 percent of all Parkinson's case, is a more intricate class which the pathogenic that underline is are not yet fully understood [11]. The occurrence rate over the age of 60 years was 247/100,000. Allow prevalence rate 27/100,000 was reported from Bangalore, in the southern part of India and 16.1/100,000from rural Bengal in the eastern part of India [12]. Gait dysfunction and postural unsteadiness represent axial major curative challenges for person with Parkinson's disease axial symptoms such as freezing of gait and posture unsteadiness are known to be dopamine resistant in PD and as such non dopergenic approaches are considered are viable [13].

Parkinson and multiple sclerosis both diseases are affected on the body movement .in that case Dalfampridine act on both the condition. They have common symptoms related to gait dysfunction .other than

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gait dysfunction they have different treatment for different disease. Clinical treatment for multiple sclerosis and Parkinson's disease include medication and physical therapy. Medication therapy generally use anti-inflammatory drug such as steroid to manage the delicate onset of disease, make use of disease modifying drug to diminish frequency and cruelty of recurrences and precise drugs are used to control the symptoms related with MS. Dalfampridine is first drug which standard by USFDA improve mobility in people with multiple sclerosis and PD patient [6]. MS patient treated with 4-AP exhibited a response rate of 29.5 percent to 80 percent the long term study [32 month] indicated that 80-90 percent of patient who initially responded to 4-APexibited long term benefit. Although improving symptoms 4AP does not inhibit the progression of MS [1].

Choice of drug

Dalfampridine is potassium channel blockers which block the potassium channel by restore the nerve impulse transmission. Blocking of potassium channel can corresponding promote and activate synaptic conduction. In normal myelinated axon concentration of sodium channel increases at the nodes of ranvier which cause action potential to propagate, conversely the area between the nodes is covered with myelin and greatest number of potassium channel, which resist the generation of action potentials. In axons that are demyelinated, action potential amplitude and duration are decreased because of the potassium channel that comes out on axon plasma membrane. Dalfampridine increases the amplitude and duration of nerve transmission resulting in enriched nerve conduction in demyelinated animal nerve [7]. Dalfampridine is the first drug that was specially accepted by United State Food and Drug Administration [FDA] on January 22, 2010 and is launched by accord therapeutics under the brand name AMPYRA. It is used in to the walking speed in patient with suffering from multiple sclerosis, gait dysfunction in Parkinson's syndrome and dementia. The FDA approved Dalfampridine orphan drug category providing 7years marked entirely for the drug [1].

Chemistry of Dalfampridine

Dalfampridine is also known as 4-aminopyridin, 4-pyradilamine, and fampridine. Dalfampridine is member of mono amino and diamino derivatives of pyridine, with molecular formula structure of C5H6N2. The pyridine ring has an amino substitution at 4th position, the molecular formula of Dalfampridine is 94.12 and important feature of dalfampridine ER that distinguish out from compounded immediate release formulation of 4-aminopyridine is it's prolong pharmacokinetic half-life. The extend release technology developed by Elan pharma International Ltd. and termed MXDAS consist of proprietary polymer matrix that control release by diffusion resulting in lower peak serum level and longer duration of action [14].

Pharmacokinetic and pharmacodynamics

In spite of a many study and theories, the exact etiology and pathogenesis of MS still remain not fully educated. One of the most widely accepted hypothesis is that MS is an inflammatory disease controlled by T cell mediated autoimmune reaction against the myelin sheet which predominately affects the white matter. In myelinated axon the blockade of fast voltages gated potassium channel has little effect on the action potential and nodal conduction demyelination alter the structural and functional relationship of voltages gated ion channel along the axonal membrane and also lead to exposure of potassium channel which impaired the action potential creation and transmission this conduction deficit contribute to the neurological defecate experienced by SCI and MS patient potassium channel blockade by 4AP Prolong the duration of the sodium channel action current, thereby increasing the safety factor for conduction on across the demyelinated internodes. Many of the early clinical application of 4APused intravenous direction or oral gelatin capsule containing the powder form 4AP triturated with lactose or microcrystalline cellulose all these immediate release formulation are characterized with short tie to peak concentration and biological half-life more recently the prolonged release tablet form of 4 AP has been developed and is standard for improve patient compliance and lower incidence and severity of unwanted side effect [15].

An oral medication, dalfampridiene is extend release formulation of 4-aminopyridine is rapidly absorb in gastrointestinal tract it has relative bioavailability is 96 percent when compared to aqueous solution [16]. In healthy volunteer who take a single 10 mg dose of dalfampridine which reaches peak concentration into 3-4 hours if dalfampridine take with the meals which increases peak concentration or action. Also this drug takes without meal. It was almost completely and rapidly eliminated of 95.5 per dose of dalfampridine by urinary excretion and remaining 0.5 per eliminated through feces dalfampridine is 97 to 99 per unbound to plasma protein elimination half-life of dalfampridine is 5.2to 6.5 hrs. in healthy individuals. As a lipid soluble agent dalfampridine passes through blood brain barrier and blocks potassium channel in both peripheral and central nervous system [5,7] while 3,4 diaminopridineis water soluble do not cross brain barrier. In vitro studied human liver microsome indicates that the enzyme cytochrome P450 2E1 [CYP2E1] play a major role in the conversion of dalfampridine to its 3 hydraoxlated metabolites. Dalfampridine has been used many years in human with various neurological condition such multiple sclerosis , Parkinson's related gait dysfunction, spinal cord injury, cerebellar ataxia and lambert etarson syndrome in two phase three clinical trials. This enhancement with a reduction in patient reported ambulatory disability and was a clinical meaningful therapeutic benefit. A treatment with 10 mg of dalfampridine twice daily improved the walking ability measured by the time 25 foot test in responder by 25 percent responder accounted by 35-45 percent. Non responder do not benefit by dalfampridine in two phase third clinical trial, a significally greater proportion of people on therapy had a consist an improvement in walking speed compared to those in placebo group. Another phase 3 multicenter clinical trial of dafampridine which was controlled and double blind included 301MS patient of different types [27%wite 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 wide dalfampridine 10mg [N =229] or placebo [N=72] orally twice dally for a period 14 weeks. 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 0r 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 safety findings in this study based on the result of this study, treatment of MS patients with a decrease in patent's gait injury. In trial first the efficacy and safety of dalfampridine for improving ambulation in adult patient with MS where investigated further in phase 3 multicenter trials conducted throughout the U.S and Canada. During the study period 300 patient were randomly assigned top revise either dalfampridine 10 mg or placebo twice daily after the 14 week treatment period patient were observed for an additional four week, enrolled patient were 18 to70 years of age with more than a two month history

of MS of any type. The average T25FW test was 8 to 45 second. A total 227 patient completed study in 14 week trial. A significantly greater proportion of patient taking AMPYRA as compared to placebo; 42.9 per vs. 9.3 per, respectively during the double blind treatment period, a significantly greater patient of proportion patient taking dalfampridine 10 mg twice daily had increased in walking speed of at least 10,20 or 30 per from baseline compared to the placebo in trial second a total of 283 subject completed the study for 21 week a significantly greater proportion of patient taking dalfampridine as compared to patient taking to placebo, 34.8per vs. 8.3 per respectively. During the double blind treatment period, a significantly greater proportion of patient taking dalfampridine 10 mg twice daily had increases in walking speed of at least 10, 20 or 30 per from baseline compared to placebo in trial 1 and 2, consistent improvement in walking speed were shown to be associated with improvement on patient self-assessment of ambulatory disability. Participants were permitted to continue all previously prescribed medication for MS {immunomodulatory] as long as they were stable with this agent for at least 60 days. Of all patient included in these trials, 63 per when revising concomitant immunomodulatory theory however it was determined that the degree of improvement in waking ability was note related to this medication. It was predictable that about 400,000 Americans were suffering from multiple sclerosis and 64-85% of patient will have difficulty in waking within 15 years of analysis. Dalfampridine is the first and only FDA approved oral drug addressing waking destruction in patients with multiple sclerosis

Side effect

Dalfampridine ER was well tolerated in PD patient the main anxiety from previous clinical experience with dalfampridine were seizures. Three subject withdraw from the trial due to adverse effect, two while on drug and one while on placebo the use of dalfampridine include urinary tract infection [D-ER 9 per, placebo 4.5 per], insomnia, dizziness [DER 18.1 per, placebo 4.5 per] these are more serious side effect- headache, nausea, asthma, black pain, impaired balance are the common adverse side effect of MS and PD.

Conclusion

Dalfampridine ER is the first of new class of pharmacotherapeutics to restore neurological function compromised by central demyelination. During the course of MS and PD the majority of patients experience waking difficulty dalfampridine occurs novel therapeutic option for these patient as demonstrated by increasing walking speed disability observe in various clinical trials. It is the safe and well tolerated agent may be used single or in combination with other MS therapies. The improvement in gait brought about by the drug evident as increased waking speed on timed waking test [T25FW].

Acknowledgement

Not applicable

Conflict of Interest

None to declare

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