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Dalfampridine: A Bioactive Compound for Improvement in Patients with Multiple Sclerosis

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Abstract

Multiple sclerosis (MS) is known as chronic autoimmune, inflammatory neurological disorder of the central nervous system which may cause progressive walking impairment which results to disability, loss of independence and diminished quality of life. Dalfampridine (4-aminopyridine), a voltage-dependent potassium channel blocker, has been shown to improve walking in patients with MS, as demonstrated by an increase in walking speed. Dalfampridine is the first drug approved by the United State Food and Drug Administration and launched by Acorda therapeutics under the trade name AMPYRA. It has been found to improve walking in patients with any type of Multiple Sclerosis. It is prepared by the decarbonylation of pyridine-4-carboxamide using sodium hypochlorite via Hoffman rearrangement. The supposed mechanism of action of dalfampridine is the restoration of axonal conduction through obstruction of the potassium channels that become open during axonal demyelination. It is the first pharmacologic remedy for this symptom and has been integrated into clinical management of MS. The present article summarizes the available updated information so far on the Dalfampridine with special prominence on its chemistry, pharmacology with detailed mechanism of action, pharmacodynamics, pharmacokinetics, metabolism and clinical trials etc.

Keywords: 4-aminopyridine; Dalfampridine; Multiple sclerosis; Walking; Disorder

Introduction

Multiple sclerosis (MS) is known as chronic autoimmune, inflammatory neurological disorder of the central nervous system (CNS) [1,2]. It is a potentially disabling disease of the brain and spinal cord which attacks the myelinated axons in the CNS, destroying the myelin and the axons to a variable degrees [3,4]. The progression of MS is highly diverse and erratic. In most patients, the disease is characterized initially by incidents of reversible neurological shortfalls, which is often followed by advanced nervous deterioration over time. The disease can be diagnosed on the basis of clinical findings and supporting evidence from ancillary tests, such as magnetic resonance imaging of the brain and examination of the cerebrospinal fluid. MS naturally occurs in adults 20 to 45 years of age; occasionally, it presents in childhood or late middle age [5]. It may be caused due to appearance of combination of genetic susceptibility and a nongenetic trigger, such as a virus, metabolism, or environmental aspects, that together result in a self-sustaining autoimmune condition that leads to recurrent immune attacks on the CNS [5].

The bioactive compound Dalfampridine (Ampyra, Acorda) is the first drug approved by the United State Food and Drug Administration in 2010 and launched by Acorda therapeutics under the trade name AMPYRA. It has been found to improve walking in patients with any type of Multiple Sclerosis [6]. In experimental studies, approximately one-third of dalfampridine-treated patients had faster walking speeds compared with placebo-treated patients [7].

Dalfampridine tablets contain a sustained-release preparation of 4-aminopyridine, which blocks potassium channels on the surface of nerve fibers [8]. This blocking ability may improve the conduction of nerve signals in nerve fibers whose insulating myelin sheath has been damaged by MS.

Chemistry

Dalfampridine (4-Aminopyridine) is a white crystalline odourless organic compound with the chemical formula $C_5H_6N_2$ and molecular weight 94.117g/mol. It is prepared by the decarbonylation of pyridine-4-carboxamide using sodium hypochlorite via Hoffman rearrangement. The pyridine carboxamide is generated from the corresponding nitrile, which in turn is obtained from the

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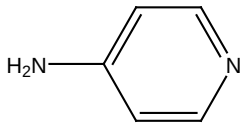
ammoxidation of 4-methylpyridine. The molecule is one of the three isomeric amines of pyridine. It is readily soluble in ethanol and soluble in benzene and ethyl ether.



4-Aminopyridine

The maximum recommended dosage is one tablet of 10-mg twice daily, taken with or without food. This dosage should not be exceeded. The tablets should be taken approximately 12 hours apart, and patients should not take double or extra doses if a dose is missed [8]. It is used primarily as a research tool, in characterizing subtypes of potassium channel, and has also been used to manage some of the symptoms of multiple sclerosis. In the laboratory, 4-AP is a useful pharmacological tool in studying various potassium conductances in physiology and biophysics. It is a relatively selective blocker of members of Kv1 (family of voltage-activated K+ channels.). At concentration of 1mM it selectively and reversibly inhibits shaker channels without significant effect on other sodium, calcium, and potassium conductances [9].

Pharmacology

Mechanism of action

Dalfampridine blocks potassium channels, on the surface of nerve fibers, which improves the conduction of nerve signals along nerve fibers whose insulating myelin coating has been destroyed by MS. It is a broad-spectrum potassium channel blocker that does not have a pharmacological effect on duration of the QRS interval and it does not prolong the QTc interval. In animal studies, dalfampridine-mediated inhibition of potassium channels increased the conductivity of demyelinated nerve fibers. Electrophysiologic studies of demyelinated axons show that augmented potassium currents increase extracellular potassium ion concentration which decreases action potential duration which may cause conduction failure. Potassium channel blockade reverses this effect. However, a recent study has shown that Dalfampridine is a potent calcium channel activator and can improve synaptic and neuromuscular function by directly acting on the calcium channel beta subunit (β_1). MS patients treated with Dalfampridine exhibited a response rate of 29.5% to 80% [10].

Pharmacodynamics

Dalfampridine is a broad-spectrum voltage-gated potassium channel blocker, which may increase duration of action potential and amplitude, leading to improved demyelinated nerve fibers and is the hallmark of some neurodegenerative autoimmune diseases, including multiple sclerosis, transverse myelitis, acute disseminated encephalomyelitis, Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy, central pontinemyelinosis, inherited demyelinating diseases such as Leukodystrophy and Charcot Marie Tooth. The metabolites have been shown to have no pharmacologic activity on potassium channels. Blocking voltage-gated potassium channels facilitates direct blocking of the synaptic and neuromuscular transmits ions conventionally and it was also suggested that Dalfampridine can directly target presynaptic high voltage-activated calcium channels to potentiate neurotransmitter release independent of potassium channels [11].

Pharmacokinetics

Dalfampridine, a sustained-release oral preparation, is rapidly absorbed, but relative bioavailability is 96% when compared to an aqueous oral solution. It gives a slower rise to a lower peak concentration C_{max} (maximum concentration that a drug achieves in the tested area after the drug has been administrated and prior to the administration of a second dose) i.e. 3–4h post administration, with no effect on the extent of absorption AUC (area under curve). When dalfampridine is taken with food, there is a slight increase in C_{max} (12–17%) and a slight decrease in AUC (4–7%). Dalfampridine was nearly completely (95.5%) and rapidly eliminated within 24h as unchanged drug via urinary excretion and 0.5% recovered in feces suggesting that it is unlikely to undergo substantial metabolic transformation with mean terminal disk position, half-life is 6.4h and plasma half life of about 7.6h in healthy individuals. Dalfampridine is largely unbound to plasma proteins (97–99%) [12].

Clinical study

It was estimated that about 500,000 persons in America were suffering from multiple sclerosis and 64–85% of patients will have difficulty in walking within 16 years of diagnosis. Dalfampridine is the first and only FDA-approved oral drug addressing walking impairment in patients with multiple sclerosis [13].

Dosage and administration

The maximum recommended dose of AMPYRA is one tablet of 10mg twice daily, should be taken with or without food. Doses should be taken approximately 12h apart. Patients should not taken double or extra doses if a dose is missed. No additional benefit was exihibited at doses greater than 10mg twice daily and adverse reactions and discontinuations were more frequent at higher doses. Tablets should only be taken as whole; do not divide, crush, chew, or dissolved. AMPYRA is contraindicated in patients with moderate or severe renal impairment. AMPYRA is contraindicated in patients with moderate or severe renal impairment (CrCl 51–80mL/min) [14].

Side effects

Urinary tract infections were the most common adverse events associated with dalfampridine during clinical trials. At the dosage greater than the recommended 10mg twice a day, dalfampridine can cause seizures, balance disorder, swelling in the nose or throat, constipation, diarrhea, indigestion, throat pain, and burning, tingling, itching of skin, insomnia, dizziness, headache, nausea, asthenia, back pain, constipation, dyspepsia, balance disorder, multiple sclerosis relapse, paresthesia, nasopharyngitis, pharyngolaryngeal pain, problems with balance, MS relapse, burning, tingling or itching of the skin, irritation of the nose and throat, constipation, indigestion and throat pain [15].

Contraindication

Dalfampridine is contraindicated in patients having moderate to severe kidney diseases because the blood levels with the drug approach those associated with the occurrence of seizures. Because of this adverse event, dalfampridine is contraindicated in patients with a prior history of seizure and should be discontinued in patients in which seizure occurs. Dalfampridine should not be consumed by pregnant women, children under 18 years of age and it should not be taken with other aminopyridine medications. Dalfampridine demonstrated efficacy in all four major types of MS, including relapsing-remitting, secondary progressive, progressive relapsing, and primary progressive, and can be used alone or in combination

with immunomodulatory drugs [16].

Proper usage

Dalfampridine should be kept out of the reach of children and should not take more than two tablets in a 24-h period. The medication can be taken with or without food but it should never chewed and crushed before swallowing because it may cause the medication to release too quickly, which may increase the risk of having a seizure. Suppose if a dose of dalfampridine is missed then never stop the therapy but continue with the next dose at your regular scheduled time [17].

Drug Interactions

Dalfampridine kinetics was not affected by co-administration of subcutaneous injections of eight million unit's interferon beta-1b. No pharmacokinetic drug–drug interaction was observed with co-administration of dalfampridine 15mg and baclofen 10mg. *In vitro* data with human liver microsomes showed that dalfampridine was not a direct or time-dependent inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5. Dalfampridine is not likely to affect the pharmacokinetics of drugs that are substrates of these enzymes. *In vitro*, dalfampridine is not a substrate or an inhibitor for the p-glycoprotein transporterThe pharmacokinetics of AMPYRA is unlikely to be affected by drugs that inhibit the p-glycoprotein transporter, and dalfampridine is not likely to affect the pharmacokinetic of drugs that are substrates of the p-glycoprotein transporter [18].

Conclusion

In the circumstance of multiple sclerosis, there is abnormality in conduction, which includes conduction delay or block due to the loss of the oligodendrocyte myelin complex which in turn results in the reorganization of axolemmal ion channels. So, the agents which block potassium channels have been investigated in the context of clinical trials with positive impact on impulse conduction in experimentally-induced demyelination in MS patients. Dalfampridine is an extended release form of 4-aminopyridine, which has been recently been 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.

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