Cleveland Clinic

Mellen Center Approaches: Use of dalfampridine (Ampyra).

What is dalfampridine and for what is it approved?

Dalfampridine (Ampyra) was approved by the FDA on January 22nd, 2010 as an oral medication to improve walking in patients with MS. Dalfampridine is a symptomatic therapy, and can be used in combination with disease modifying agents. It is an extended release form of 4-aminopyridine (4-AP, also known as fampridine).

Dalfampridine is a broad-spectrum inhibitor of voltage-sensitive potassium channels. In laboratory studies, dalfampridine has been found to improve impulse conduction in demyelinated nerve fibers and to increase synaptic transmitter release at nerve endings. (Judge, 2006). Its mechanism of action in vivo has not been determined.

Dalfampridine is administered as a 10 mg extended release tablet every twelve hours. In two phase III trials in patients with MS randomized to dalfampridine vs. placebo, a significantly greater percentage of patients were 'responders' on dalfampridine than on placebo (Goodman et al, 2008; Goodman et al 2009).

A responder was defined as a patient who consistently showed faster walking speed on the Timed 25 Foot Walk (T25FW) while on therapy than while not on therapy. About 1/3 patients responded to dalfampridine in these studies (Goodman et al, 2009). There was also improvement of scores on the MS-Walking Scale 12, a patient-reported measure of walking performance in daily activities, in dalfampridine responders.

In a phase IIIb clinical trial comparing 10 mg twice daily versus 5 mg twice daily dosing or placebo, the 5 mg dose failed to demonstrate efficacy. With the standard dose of 10 mg twice daily, there was again a statistically significant effect on walking speed (T25FW) using the 'responder analysis'.The study also showed a significant effect on the 6-minute walk test (a measure of walking endurance) with 10 mg twice daily.

What is the difference between dalfampridine and compounded 4-aminopyridine?

Dalfampridine is an extended-release formulation of 4-AP, while compounded 4-AP is mostly an immediate release (IR) formulation. The IR formulation leads to an initial peak in plasma concentration, which has been associated with a higher risk of side effects. In addition, there have been reports of accidental overdose due to compounding errors. Patients should be instructed to never take dalfampridine and compounded 4-AP concomitantly.

Who should be considered for dalfampridine?

Reasonable candidates to try dalfampridine are patients with any type of MS who have walking problems from MS and for whom an improvement in walking would be of clinical benefit. In phase III clinical trials, the increased response rate in the dalfampridine group was observed across all four major types of MS (relapsing remitting, secondary progressive, progressive relapsing and primary progressive), and there was no difference in response based on baseline disability status.

We note that the magnitude of effect of dalfampridine is usually modest, although significant to the patient. We would not expect patients to change the type of assistive device that they use (that is, if they are using a Rollator, we would not expect them to switch to a cane or no device due to dalfampridine). The average increase in walking speed reported in the clinical trials was around 25% (a 20% change on 25 foot timed walk was found to be the minimal clinically important change for patients). Dalfampridine is not expected to restore ambulation in MS patients who are wheelchair-bound.

Other functions might improve (for example upper extremity function, visual acuity, diplopia), but this was not proven in the pivotal trials.

continued on next page

13-NEU-530

Mellen Center Approaches: Use of dalfampridine (Ampyra), continued

Are there any types of gait disturbance for which dalfampridine is not indicated?

There is no formal limitation for dalfampridine use regarding the specific type of gait abnormality, but we expect it will be more beneficial in patients with spastic paresis over those with mostly cerebellar or sensory ataxia. It is essential to remember that dalfampridine does not address all gait problems. For example, dalfampridine does not improve gait stability or obviate the need for assistive device and/or physical therapy, so we recommend these be addressed first, since prescribing a medication that increases walking speed in a patient with unsafe gait may lead to increased risk of falling.

How is dalfampridine dosed?

There is one dosage, 10 mg tablet twice a day, taken with or without food. Doses should be approximately 12 hours apart. PATIENTS SHOULD NOT DOUBLE UP DOSES IF THEY MISS A DOSE to reduce the risk of side-effects, including seizures. There was no additional benefit above this dose in clinical trials, and serious side effects including seizures were more common at higher doses. Tablets should be taken whole, not crushed or chewed.

There is no data on use in pediatric age groups and this medicine is therefore not recommended at present for patients younger than 18 years of age. Data in the elderly is not available. Dalfampridine should not be used by women who are pregnant or nursing. Based on animal data, this medicine may cause fetal harm.

When would you expect to see an effect from dalfampridine?

We would expect to see a response within 2-4 weeks. This is a medication which should have its maximal effectively rapidly and thus prolonged trials beyond a month are not helpful, unless a medical event prevents the patient and the clinician from assessing the true effect of the medication (e.g. UTI, MS exacerbation).

What are the risks of dalfampridine and what can be done to reduce those risks?

The FDA approved dalfampridine with a risk evaluation and mitigation strategy (REMS) program comprising a medication guide and communication plan. The goals of the communication plan are to inform patients about the serious risks, including seizures (which are associated with use of higher than recommended doses of dalfampridine therapy) and the change of the established name from fampridine to dalfampridine.

Detailed information about prescribing dalfampridine is available from the following website:

http://ampyra-hcp.com/hcp/all_about_ampyra/prescribing_information/

Dalfampridine is contraindicated in patients who have previously had seizures, and may cause seizures de novo, particularly at higher than recommended doses. The overall incidence of seizures with dalfampridine 10 mg twice daily is 0.4 per 100 person-years.

It is also contraindicated in patients with moderate to severe renal impairment (creatinine clearance $\leq$ 50 mL/min). It should be used with caution in patients over 50 years of age, who are at higher risk of having mild renal impairment. Over 90% of the drug is excreted in the urine, and the safety of dalfampridine is currently unknown in patients with mild renal impairment. The estimated creatinine clearance should be calculated in all patients prior to starting treatment, and should be monitored at least yearly. It is necessary to know the patient's weight to calculate the estimated creatinine clearance.

Other reported side effects seen at $\geq$ 2% of dalfampridine-treated patients in treatment trials included the following: urinary tract infection, insomnia, dizziness, headache, nausea, asthenia, back pain, balance disorder, paresthesia, nasopharyngitis, constipation, dyspepsia, and pharyngolaryngeal pain. Several anaphylactic reactions temporally related with taking dalfampridine were also reported.

Dalfampridine should not be used along with other forms of 4-aminopyridine. For example, patients who are currently on compounded 4-AP must stop the compounded medication before starting dalfampridine.

What about doing an EEG prior to beginning dalfampridine?

A history of prior seizures is a contraindication for starting dalfampridine. All participants in the licensing clinical trials for dalfampridine received screening EEGs and were excluded if there was evidence for epileptiform activity on that screening EEG. Therefore, there is no published experience of dalfampridine in

continued on next page

Mellen Center Approaches: Use of dalfampridine (Ampyra), continued

patients with epileptiform activity on screening EEG. However, the utility of a screening EEG is unclear. Therefore, obtaining an EEG before prescribing dalfampridine is at the discretion of the clinician.

What is the process to prescribe dalfampridine?

Information on prescribing dalfampridine can be obtained at the following website:

http://www.ampyra.com/hcp/

Dalfampridine is presently available only through a specialty pharmacy. Specific forms need to be submitted with insurance information for dalfampridine approval.

What else should I consider when prescribing dalfampridine?

Walking is a complex neurobiological function and there are many ways that we can improve walking skills beyond the use of dalfampridine. When prescribing dalfampridine, we recommend a comprehensive approach to walking limitations. We think that patients should be assessed by a physical therapist skilled at gait assessment. PT exercises aimed at improving strength, spasticity, gait, and balance, and the provision of walking aides (cane, Canadian crutches, walker, Rollator, etc.) and/or bracing (for example ankle foot orthosis) may significantly improve gait efficiency and safety.

REFERENCES:

Bever CT, Judge S. Sustained-release fampridine for multiple sclerosis. Expert Opinion Investig. Drug. 2009;18:1013-1024

Burton JM, Bell CM, Walker SE, O'Connor PW. 4-aminopyridine toxicity with unintentional overdose in four patients with multiple sclerosis. Neurology 2008;71:1833-4.

Goodman AD, Cohen JA, Cross A, et al. Fampridine-SR in multiple sclerosis: a randomized, double-blind, placebo-controlled, dose-ranging study. Multiple Sclerosis 2007;13:357-368

Goodman AD, Brown TR, Cohen JA, et al. Dose comparison trial of sustained-release fampridine in multiple sclerosis. Neurology 2008;71:1134-41

Goodman AD, Brown TR, Krupp LB, et al. Sustained-release oral fampridine in multiple sclerosis: a randomized, double-blind, controlled trial. Lancet 2009;373:732-738

Judge SIV, Bever CT. Potassium channel blockers in multiple sclerosis: neuronal Kv channels and effects of symptomatic treatment. Pharm Ther 2006;111:224-59

Koch M, Uyttenboogaart M, Polman S, et al. Seizures in Multiple Sclerosis. Epilepsia 2008;49:948-953