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DALFAMPIRIDINE (4-AMINOPYRIDINE) TOXICITY IN MULTIPLE SCLEROSIS: A CASE REPORT.

Medicine

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ABSTRACT

Dalfampridine (4-aminopyridine) is a newer drug being used for Multiple sclerosis (MS) which is an immune mediated inflammatory disease affecting Central Nervous System. Dalfampridine by virtue of blocking potassium channel widens the action potential and enhances the muscle strength. Most common side effect of Dalfampridine is Seizure and this is dose dependent. The treatment of patients with Dalfampridine overdose is supportive. We report a case who accidently ingested Dalfampridine 5 times than the daily recommended dose and presented to us with seizures.

KEYWORDS

Multiple sclerosis (MS), Diseases modifying therapies (DMT), Dalfampridine (4-aminopyridine) -4-AP.

INTRODUCTION

Multiple sclerosis (MS) is a potentially disabling disease of the brain and spinal cord (central nervous system). It is an immune-mediated inflammatory disease leading to loss of the protective myelin sheath that covers axons, causing fleeting neurologic deficits.[1] Currently there is no definite cure for MS, but many diseases modifying therapies (DMT) have been tried and are still being developed. Dalfampridine, or 4-aminopyridine (4-AP) is one of newer medication approved by FDA United States in January 2010 which help patients with MS improve their gait and strength while walking.[2] Dalfampridine selectively blocks voltage-gated potassium channels, thereby blocking potassium efflux which is required for repolarization following action potential, widens action potential and subsequently enhances interneuronal and neuromuscular synaptic transmission. This ability of Dalfampridine to reverse synaptic blockade has been used as possible novel treatment in many different neuromuscular disorders such as Alzheimer's disease, Botulism, Eaton Lambert Syndrome and Multiple Sclerosis.[3] Dalfampridine overdose has been shown to have neuroexcitatory features- hyperexcitability, tremors, muscle incoordination, hypersalivation, convulsions, along with cardiac or respiratory distress.[4]

Here we report first case of a Dalfampridine overdose in INDIA.

Case Report

A 43-year-old female with a past medical history of MS was brought into the emergency department (ED) by Emergency Medical Services after she had complaints of generalized weakness with 2-3 episodes of vomiting, restlessness and hiccups. Patient had history of having consumed 10 tablets of Dalfampridine 10 mg each for the first time about 5-6 hours prior to the symptoms have started.

Other than MS, the patient had no other pertinent past medical history. Her current medications were Multivitamins and Baclofen tablets (all part of his MS treatment regimen). The initial vital signs in ED were as follows: Blood pressure: 130/82 mmHg; Heart rate: 94/min; Respiratory rate: 20/min; Temperature: 97.4 °F ; O_2saturations: 98% on room air. The blood glucose was 109 mg/dl. The patient was conscious, lethargic, following simple commands. There were no focal deficits. Her pupils were 3 mm, equal and reactive and her mucous membranes were moist. She was hemodynamically stable. Intravenous access was established, labs were drawn and the patient was started on maintenance intravenous normal saline. Soon after arrival, the patient had a tonic-clonic seizure, lost consciousness, her oxygen saturation decreased to below 90%. The patient was administered bolus of Midazolam 4 mg intravenous, with seizure resolution. Her trachea was intubated and subsequently placed on propofol infusion. Loading dose of one-gram Injection Levetiracetam was given.

Patient was transferred to Intensive Care (ICU) for further management. Her CT Brain was found to have no abnormality. Her initial Lab values showed-Hemoglobin-12.4 gm/dl white blood cell count of 7.7×103/mL, platelets-330/cu mm, serum sodium-140 mEq/L, potassium 4.1 mEq/L, chloride 106 mEq/L, S calcium-9.85 mg/dl bicarbonate of 22mEq/L, a blood urea-24.2 mg/ dL and a creatinine of 0.6 mg/dL. The lactic acid was 4.6 mg/dl. Total creatinine kinase was 485 units/L. Liver function tests and coagulation studies were all within normal limits. Ethanol, acetaminophen and salicylate levels were all negative. Urine toxicology screen was negative. An arterial blood gas showed pH 7.44, pCO_2 32, pO_2 122 and HCO_3 23 (performed immediately after intubation). The electrocardiogram showed a sinus rhythm at 94 beats per minute. 2D ECHO was within normal limits. There was no epileptiform activity in EEG. The patient was extubated on hospital day 2. She was discharged on Hospital day 5, with normal mental status and neurologic exam with advice to review after 5 days or earlier in case of emergency.

DISCUSSION

Since Dalfampridine being less commonly used, its toxic effects are not clear and are still being evaluated.First cases of acute Dalfampridine toxicity were reported in 1978 in manufacturing employees.[5]

Dalfampridine had shown improvement in both walking speed and function in patients with MS Oral, daily recommended dose is 10 mg twice per day.[6]

It has been observed that this therapeutic action leads to adverse outcome in higher doses.[7]

Neuroexcitatory adverse effect- seizures is one of most reported manifestation of Dalfampridine toxicity and this can progress to status epilepticus. Several studies have shown odds of seizures to be directly dependent on amount of dalfampridine ingested.[8] CNS area responsible for cognition and memory has also been shown to be adversely affected due to Dalfampridine toxicity.[9]

When serum Dalfampridine concentrations is measured a level of 30-475 ng/mL has been associated with high chances of seizures.[10] However there are reports which has shown contrasting results. Based on the available literature, serum Dalfampridine concentrations appear helpful in establishing exposure yet unreliable in accurately assessing clinical toxicity.[11]

Our lab did not have facility to do Dalfampridine drug assay levels so we could not get serum concentration of the drug. But based on the medication history and clinical presentation, our patient identifies with the similar cases of Dalfampridine overdose adverse reaction in the form of seizures as mentioned in several case reports.

Drug Literature warns of most common side effect of Dalfampridine overdose being seizure. Risk of seizure have been shown to increase by 4 times when the ingested dose is increased to 50% more than the daily recommended dose.[12]

CONCLUSION

Newer and more effective drug is the need of the hour for crippling diseases like MS. But safety profile should be clearly understood and strictly warned to the patients before prescribing. Literature is replete with clinical trial and clinical profile of Dalfampridine, including its toxic effects. We recommend refraining prescribing and ingesting Dalfampridine over and above the recommended doses and patient should be clearly educated about its side effects.

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