

Recent Advances in Clinical Trials

Abruptly Stopping an Adamantane Management for Fatigue in an Elderly Multiple Sclerosis Patient Provoked Acute Withdrawal Symptoms (AWS); A Case Report

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ABSTRACT

Introduction: Health care workers are continuously being burdened with acute conditions especially with the current pandemic of Covid-19. Staying home and feeling trapped can be particularly detrimental to patients with history of depression or psychotic as well as multiple sclerosis. We present a case of a 64-year-old patient with Multiple Sclerosis whose condition is being managed with mainly an antiviral drug and dopamine promoter. Withdrawal symptoms arose acutely after abrupt cessation of the medication. Adamantanes are thought to work by raising the amount of dopamine available to brain cells. The purpose of this research is to report a case of a 64-year-old multiple sclerosis female patient who presented with Acute Withdrawal Syndrome (AWS) after being managed with an antiviral drug and dopamine promoter for two years and abruptly stopping the medication.

Case Presentation: A 64-year-old woman with past medical history of stroke and multiple sclerosis reported symptoms of AWS after abruptly stopping an adamantane use for multiple sclerosis. The patient was on cyclobenzaprine for spasticity, gabapentin and lamotrigine for neuropathic pain and seizure disorder respectively. She also had a history of hypertension and hyperlipidemia and presented with 1-week history of nausea and vomiting followed by visual hallucination, tremor, slurred speech and lethargy. On presentation, the patient was afebrile and hemodynamically stable. This patient denies blurred vision and severe fatigue with bathing or exercise. Upon further evaluation, patient did not report electrical sensation down her limbs or back especially with neck flexion. The initial labs were remarkable for hemoglobin of 8.5mg/dL and hypokalemia of 3.2mmol/L. We suspected vasculitis of CNS. One of the proposed pathophysiology for this is the extensive inflammatory damage to the blood brain barrier, allowing inflammatory cell recruitment into the CNS. The patient was admitted for acute altered mental status with waxing and waning symptoms. Her acute delirium symptoms lead to the withdrawal of amantadine and cyclobenzaprine. Within about 48-70 hours later, patient developed severe agitation requiring emergent intubation.

EEG showed generalized medium voltage delta and theta and fast activity throughout indicative of diffuse cerebral dysfunction, but no lateralized or epileptic activity was seen. CT brain was negative for acute stroke or bleed. The patient underwent lumbar puncture, and was started on empiric coverage with IV acyclovir, vancomycin, and

ceftriaxone for possible meningoencephalitis along with methylprednisolone for possible multiple sclerosis flare vs autoimmune encephalitis. MRI showed stable extensive white matter T2 hyperintense lesions. CSF was negative for infectious processes, and vancomycin, ceftriaxone, and acyclovir were discontinued. The patient continued to require sedation for severe agitation. The severe agitation was suspected to be due to discontinuation of her home medications, one of which was the adamantane; amantadine. The amantadine was resumed with improvement of her mental status within 24 hours. Patient was extubated within 48 hours of initiation of amantadine and was transferred to the floor for continuity of care and eventually discharged home after 15 days of hospitalization.

Conclusion: Acute Withdrawal Syndrome (AWS) symptoms are often as a result of abrupt cessation of a medication(s) particularly central acting agents like clonidine, beta adrenergic antagonists as well as diuretics but Amantadine is starting to be a strong culprit since it is also thought to act centrally as a dopamine agonist. Clinicians should always be mindful of AWS especially from patients on long term central acting medications that have been abruptly stopped.

Keywords

AWS, Adamantane, Multiple Sclerosis, Elderly female patient, Inflammation, Acyclovir.

Introduction

Symptoms of AWS includes severe delirium with agitation, hallucinations, anxiety, paranoia, tremor, slurred speech, or stupor. Typical symptoms of Multiple Sclerosis (MS) include sensory disturbances, motor weakness, optic neuritis (monocular visual impairment with pain), Lhermitte sign (electrical sensation down the spine on neck flexion), fatigue, and impaired coordination. Patients may also present with or develop pain, depression, sexual dysfunction, bladder urgency or retention, and bowel dysfunction. And the signs of MS include Ataxia, decreased sensation (pain, vibration, position), decreased strength, hyperreflexia, spasticity, Nystagmus, visual defects (internuclear ophthalmoplegia, optic disc pallor, red color desaturation, reduced visual acuity) [1].

Amantadine is an anti-influenza agent as it inhibits replication of influenza A viruses. However, the first evidence of improved fatigue in MS was from a patient treated with amantadine for influenza prophylaxis. Its activity on glutamate receptors has also been shown. The mechanism of the potential action of amantadine for fatigue remains unclear. An antiviral activity, an immunologically mediated action, or an amphetamine-like action have been suggested. Since 1987, some benefits of amantadine have also been reported by randomized, double-blind, placebo-controlled trials. As a consequence, many textbooks report amantadine as a first-choice drug for MS-related fatigue [2].

Although many drugs have been tested in multiple clinical trials, only those trials with amantadine have provided enough evidence to allow the recommendation of this treatment for MS-related fatigue. Yet its effect is moderate and the quality of that evidence may be considered as low to moderate, according to the NICE guidelines. Its main mechanism of action is not yet fully understood, although its effects in fatigue seem to be related to its dopaminergic effects, supporting the dopamine imbalance theory for MS-related fatigue abovementioned. To date, at least seven randomized clinical trials (RCTs) have compared amantadine with placebo and one RCT has compared amantadine with aspirin. In general, all trials that compared amantadine with placebo showed

a significant effect of amantadine on fatigue [3].

Discussion

Discontinuation of amantadine is thought to create a functional dopamine shortage in cortical and limbic structures. The main predictors of amantadine withdrawal symptoms- waxing/waning sensorium, formication, agitation, and insomnia include being elderly, presence of advanced multiple sclerosis, and duration of amantadine therapy for longer than one year [4]. This patient with AWS presented with severe delirium with agitation, hallucinations, anxiety, paranoia, tremor, slurred speech, and stupor. These symptoms resolved upon re-introduction of amantadine within few hours.

Amantadine was originally used as antiviral medication for the treatment of influenza A. In the central nervous system, amantadine increases dopamine release and decreases dopamine reuptake, thereby used in the treatment of fatigue in multiple sclerosis patients. Abrupt discontinuation of amantadine can cause severe amantadine withdrawal syndrome and may be under-recognized by clinicians and this may lead to unfavorable outcomes. Amantadine is the only oral treatment that is currently recommended by the National Institute for Health and Care Excellence (NICE) for the treatment of MS-related fatigue [3].

Mitoxantrone was indicated for secondary progressive MS, worsening relapsing MS, and progressive relapsing MS. Interferon preparations and glatiramer acetate showed some delay and superiority in reducing relapses and improving MRI outcomes for high-dose/high-frequency interferon beta compared with weekly interferon beta-1a. Two other separate head-to-head trials of interferon beta and glatiramer acetate showed a similar effect on relapse outcomes [5,6].

Patient became fatigue which is extremely common in MS patients. In general, fatigue may affect up to 80% of people with MS [7-9], and can be severe in up to 65–70% of them. Importantly, it tends to persist over time once it appears. It can have an important impact on the quality of life for people with MS, and, in some cases, can be perceived as disabling as loss of power in the limbs or walking issues. Of note, fatigue does not appear more frequently in those people with progressive forms of MS, especially PPMS, but instead

it is more commonly reported amongst non-stable patients with relapse-onset MS, suggesting that its appearance is not necessarily related to objective neurological progression [10].

Conclusion

AWS is rarely reported in literature. When AWS does occur, its symptoms are often as a result of abrupt cessation of a medication(s) particularly central acting agents like clonidine, beta adrenergic antagonists as well as diuretics but Amantadine is starting to be a strong culprit since it is also thought to act centrally as a dopamine agonist. Clinicians may substitute or remove some medications from a list of administered medications based on how well the patient might be doing and also to decrease side effects that some of these medications may pose especially when given as combinations with others. Complications including stroke, encephalopathy, MI and sudden death should prompt clinicians about Acute Withdrawal syndrome particularly when patients are abruptly taken off central acting medications administered to the patient for a time period of greater than six months to a year or even more.

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