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A Case Report of Serotonin Syndrome with Venlafaxine Extended Release

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Abstract

Serotonin syndrome have been described with SSRI, SNRI and other class of antidepressants. Venlafaxine which has main actions of serotonin and norepinephrine reuptake inhibition. Mechanism of blockade of dopamine receptors and thereby inhibition of dopaminergic function by serotonin reuptake inhibition has also been hypothesized. Life threatening condition of serotonin syndrome has been reported with the single drug venlafaxine many times in the literature. Sixty seven year old man, with primary school education, who was a farmer, from a middle class family premorbid well-adjusted with no medical co-morbidities and history of episodic illness suggestive of depression for the last four years on medication(citalopram 40mg/day and vilazodone 20 mg /day for last ten months),who was prescribed newly with venlafaxine extended release 75mg per day later increased to 150 per day presented with diaphoresis, confusion, restlessness, disturbed sleep, decreased talk, urinary and fecal incontinence ,elevated blood pressure, tachycardia ,rigidity, tremor, oral dyskinesia and investigations revealed, leukocytosis, neutrophilia-mild elevation. Patient was treated symptomatically with the removal of the offending agent and cyproheptadine 8 mg /day. Patient gradually improved within three to four days.

Keywords: venlafaxine, depression, serotonin, dopamine

INTRODUCTION

Serotonin syndrome is a life-threatening condition which is iatrogenic has been underreported. Once treatment is instituted, the serotonin syndrome typically resolves within 24 hours, but confusion can last for days, and death has been reported. serotonin abundance as a clinical issue in people was first noted by Oates and Sjostrand. He revealed patients who had syndrome after getting tryptophan while on treatment with a monoamine oxidase inhibitor (MAOI). Insel portrayed two further cases in patients getting a MAOI and a tricyclic antidepressant. In 1991, Sternbach explored 38 cases from 10 case reports in which he inferred analytic measures for what was named the serotonin syndrome. Whenever more than one serotonergic agent is used, especially in the presence of comorbid medical illness and other medications, the patient should be closely monitored for the symptoms of serotonin syndrome.[1,2] The presumed pathophysiological mechanism involves brainstem and spinal cord activation of the 1A form of serotonin (5-hydroxytryptamine, or 5-HT) receptor. Serotonin syndrome is common in drug combinations involving selective serotonin reuptake inhibitors (SSRIs) like fluoxetine and drugs such as tricyclic antidepressants, monoamine oxidase inhibitors (MAOI), amphetamine, lithium, buspirone, tramadol, dextromethorphan, linezolid etc. Discontinuation of the suspected serotonergic agent and institution of supportive measures are the primary treatment, although 5-HT receptor antagonists may also play a role. Serotonin syndrome is one of such potentially life-threatening complications which usually results from use of more

than one pro-serotonergic agents. It is commonly characterized by agitation, tremors, shivering, diarrhea, hyperreflexia, hyperthermia, ataxia, and altered sensorium.[3,4,5.]

CASE REPORT

Sixty-seven-year-old man, with primary school education, who was a farmer, from a middle-class family. He was premorbidly well-adjusted. He has no chronic medical co-morbidities except for benign prostatic hypertrophy which is of mild grade and not on any medications. He has a history of episodic illness for last four years and on treatment for 10 months. There is no history of any manic or psychotic symptoms. There is no history of obsessive and compulsive symptoms. There is no history of any substance abuse, head injury and seizures. Patient was on citalopram 40mg/day and vilazodone 20 mg /day for last ten months for his depressive syndrome for which he has less than 25 percent improvement in symptoms so discontinued a few days before presenting to our department. He was diagnosed with recurrent depressive disorder currently in severe depression without psychotic symptoms.

On examination the patient was cognitively intact. He has no neurological symptoms and other systemic examination was within normal limits. Mental status examination showed depressive and anxious cognitions and somatic preoccupations. He was prescribed with venlafaxine extended release 75mg, 3 weeks later increased to 150 mg. He further presented with diaphoresis, confusion and restlessness, disturbed sleep, decreased talk, urinary and fecal incontinence, and diarrhea. The symptoms started and evolved within 2 day's time.

On this presentation the patient was oriented to time, place, person. Cognitive evaluation was within normal. Mental status examination showed prominent depressive cognitions with perplexed mood. Patient was worried about his new symptoms and was complaining of non-improvement in his overall symptoms. Neurological examination showed rigidity, hyperreflexia in all four limbs, tremor and oral dyskinesia, Vitals showed elevated blood pressure and tachycardia. Investigations revealed, leukocytosis, neutrophilia-mild elevation and mildly elevated CPK.Serotonin syndrome was provisionally diagnosed. Patient was treated symptomatically with the removal of the offending agent and empirically started on cyproheptadine 8 mg /day in divided doses. Patient showed drastic improvement in autonomic and neurological symptoms. Patient gradually improved within three to four days.

DISCUSSION

The other differentials which should be discussed are NMS, i.e., neuroleptic malignant syndrome and malignant hyperthermia. NMS is exclusively caused by dopaminergic drugs and symptoms develop over days and resolve over days to weeks. Malignant hyperthermia is a life-threatening condition that results from a genetic susceptibility to volatile anesthetics such as halothane and neuromuscular blocking drugs such as succinylcholine). In this case there was no recent exposure to antipsychotic drugs or anesthetic drugs. Hence, it is vital that clinicians should be aware of the potential of serotonin syndrome when serotonergic impact on the brain on introduction of a new antidepressant.[6] The cases of serotonin syndrome have been reported with sertraline, fluoxetine, trazodone, and venlafaxine abuse.[4,5,6] This case report highlights that venlafaxine as a substrate of CYP 2D6.Another drugs is the citalopram and vilazodone as an inhibitor of CYP 450 enzymes 2C9, 2C19, 2D6 and 3A4 which impair enzyme 2D6's ability leading to serotonin syndrome. It usually starts with muscular rigidity followed by hyperthermia and altered consciousness.[7,8]

The clinical presentation is usually marked by the triad of cognitive/behavioral changes (e.g., confusion, agitation, lethargy, coma), autonomic instability (e.g., hyperthermia, tachycardia, diaphoresis, nausea, vomiting, diarrhea, dilated pupils), and neuromuscular changes (e.g., myoclonus, hyperreflexia, rigidity, trismus). Sternbach's criteria and the Hunter Serotonin Toxicity Criteria can be used to diagnose serotonin syndrome in research and clinical setting. Some of the clinical features suggested as typical of serotonin toxicity by Sternbach are non-specific. They have been developed based on case reports and small case series. These would also be commonly observed in many other conditions such as anticholinergic delirium, and alcohol and drug withdrawal states. Hunter Serotonin Toxicity Criteria, which require the presence of one of the following features as spontaneous clonus; inducible clonus with agitation or diaphoresis; ocular clonus with agitation or diaphoresis; tremor and hyperreflexia; or hypertonia,

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temperature above 100.4° F (38° C), and ocular or inducible clonus. Patient's improvement within 48 to 72 hours of stopping the offending drugs and putative conservative treatment justified the diagnosis of serotonin syndrome. However, in NMS there is an idiosyncratic reaction to several antipsychotic drugs or removal of exogenous dopaminergic agonists. The effect of one drug altered by another via physiological mechanism such as augmentation of same neurotransmitter pathway (e.g., A strong clinical suspicion, known exposure to serotonergic agents, demonstration of specific signs and symptoms, and exclusion of other medical and psychiatric conditions are required for the diagnosis[8,9] Serotonin syndrome can be a serious complication of treatment with selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), and other serotonergic medications. There are case reports with SSRI being the culprit in majority of the cases. [5]This case presents the occurrence of serotonin syndrome in elderly male with mild prostatic hypertrophy who was on poly pharmacy with two antidepressants and sudden change to another class of serotonergic antidepressant and resultant pharmacokinetic effects. Similar cases with Venlafaxine as the offending agent have been reported previously[4,6] Elderly co morbidities can precipitate underlying genetic predisposition for serotonin syndrome.

First-line management of serotonin syndrome is withdrawal of the offending drugs and provision of supportive care. Benzodiazepines can be used to control agitation. Patients may also benefit from cyproheptadine, olanzapine or chlorpromazine. Cyproheptadine, a serotonin 2A antagonist, is commonly recommended and is the most widely used antidote. A starting dose of 12 mg should be considered, followed by an additional 2 mg every two hours if symptoms continue. After the patient is stabilized, a maintenance dosage of 8 mg every six hours may be administered. Although cyproheptadine is widely used, definitive evidence is lacking on its effectiveness in serotonin syndrome.[7,8,9] There a several cases which have shown improvement with cyproheptadine. Cyproheptadine is used to treat moderate to severe cases of serotonin syndrome. Prevention of serotonin syndrome begins with awareness of potential for toxicity from serotonergic drugs. Avoiding the combined use of serotonin-augmenting drugs. Physicians should modify prescribing practices to decrease polypharmacy and a high probability of inducing serotonin syndrome.[10,11,12.]

CONCLUSION

Although reports of acute drug reactions are common in elderly, this case points to the rule of pharmacotherapy in old age, start low and go slow. Elderly often requires half the initial starting dose as that of usual starting dose. Serotonin syndrome presenting acutely with SNRI, i.e., venlafaxine in an extended-release formulation needs to be cautious in future prescriptions. The concept of polypharmacy should be discouraged in elderly. Environmental and genetic factors are also given due importance in elderly presenting with serotonin syndrome.

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