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Case Report

Serotonin syndrome due to fluoxetine and tramadol in renal impaired patient

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ABSTRACT

Serotonin syndrome causes confusion or altered mental status; other symptoms include myoclonus, shivering, tremors, diaphoresis, hyperreflexia, incoordination, fever and diarrhoea. Tramadol possesses dual pharmacological effects i.e., a weak opiate agonist at mu, kappa and delta opiate receptors along with reuptake inhibition of norepinephrine and serotonin. Risk associated with tramadol increases when co-administered with serotonergic antidepressants or MAOIs (monoamine oxidase inhibitors) and in renal impaired. The incidence of this syndrome is less than 1% as most of the cases remain unreported. The case highlights the fact that interaction between serotonergic agents like fluoxetine and tramadol especially in the presence of co-morbid medical illness can lead to serotonin syndrome.

Keywords: Serotonin syndrome, SSRIs (Serotonin Reuptake Inhibitors), Opioids, Drug-drug interactions, CYP 450

INTRODUCTION

Serotonin syndrome is one of such potentially life threatening complications which usually results from use of more than one pro-serotonergic agents.[1,2] It is commonly characterized by agitation, tremors, shivering, diarrhea, hyperreflexia, hyperthermia, ataxia, and altered sensorium. 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.[2,3] Tramadol is an opioid analgesic having partial mu agonist activity and affects serotonin and norepinephrine neurotransmitters.[4] 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. Once treatment is instituted, the syndrome typically resolves within 24 hours, but confusion can last for days, and death has been reported.[5] 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.[6]

CASE REPORT

A 79 years old female was brought to psychiatry department of Rajindra Hospital attached to Govt. Medical College, Patiala for consultation with altered mental status and agitation. She had a history of pain at the back that radiates to lower abdomen, weakness, malaise, sadness of mood, decreased appetite, low energy, decreased ability to think and insomnia but no history of any guilt or suicidal ideation, plan or attempt for the last one month. She was assessed on MADRS (Montgomery- Asberg Depression Rating Scale)[7] rating scale with score of 12 indicating moderate depression. She took medicine consultation for her symptoms from a private practitioner. Patient was advised ultrasound for whole abdomen which showed bilateral hydroureteronephrosis grade II with increased cortical echogenicity of kidneys. Her renal function test showed mild renal impairment with GFR of 71ml/min/1.73 m^2 (60-89 ml/min/1.73 m^2). Her other routine laboratory investigations were unremarkable except anaemia (Hb- 9 gm/dl) on blood haemogram. She was prescribed capsule fluoxetine 20 mg per day for her depressive symptoms which continued for two weeks along with conservative treatment for hydroureteronephrosis. After two weeks on fluoxetine, she complained pain and was prescribed tablet tramadol 50 mg s.o.s. After taking of drugs (i.e., fluoxetine with tramadol) within about 4 hours **s**he reported to the emergency department of Psychiatry with altered mental status. Her physical examination was significant for tachycardia, hypertension, tachypnea, elevated body temperature, generalized anxiousness and transient visual hallucinations. There were generalized tremors, marked rigidity in limbs and excessive sweating. There was possibility of differential diagnoses to the serotonin syndrome i.e., neuroleptic malignant syndrome (NMS) or malignant hyperthermia. However, there was no recent use of antipsychotic drugs, benzodiazepine use or SSRI/tramadol overdose or removal of exogenous dopaminergic agonists or exposure to anaesthetic drugs (e.g., succinylcholine etc). The various lab tests of the patient including complete blood count, blood gas analysis and ammonia level, urine culture examination, CT Head, EEG etc. were negative. Her creatinine phosphokinase N-acetylcysteine CPK (NAC) was also within normal limit i.e., 95 µ /l (Normal reference range for female: 24 to 170 µ/l). On mental status examination, patient had clouding of consciousness, was disoriented to time, place and person and had transient visual hallucinations with Glasgow coma scale (GCS) score 11/15; suggestive of acute onset delirium. A provisional diagnosis as assessed on International Classification of Diseases-10 (ICD-10) was F05.0 organic brain disease specifier: Delirium due to drug interaction with possibility of serotonin syndrome. The specified drugs were stopped and supportive treatment (intravenous fluids, antipyretics etc.) and cyproheptadine 4 mg orally was given. Within the next 24 hours, patient's condition improved, her vitals were stable, she regained full consciousness and became well oriented to time, place and person with Glasgow coma scale (GCS) score 15/15.

DISCUSSION

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.[2] This case presents the occurrence of serotonin syndrome in elderly female with mild renal impairment either due to pharmacokinetic (i.e. interference with elimination) or pharmacodynamic (drug-drug interactions) i.e. the effect of one drug altered by another via physiological mechanism such as augmentation of same neurotransmitter pathway (e.g. a serotonergic drug fluoxetine and tramadol, which is partial mu agonist, with serotonin and norepinephrine activity).[4] There was history of recent intake of drugs in a patient with impaired renal function due to bilateral hydroureteronephrosis grade-II and decreased renal elimination or the degree of enzyme inhibition CYP 450 by fluoxetine that may increases toxicity. There are potential dangers of simultaneously administering drugs. Patient's improvement within 24 hours of stopping the offending drugs and putative conservative treatment justified the diagnosis of serotonin syndrome. 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. 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, diarrhoea, dilated pupils), and neuromuscular changes (e.g., myoclonus, hyperreflexia, rigidity, trismus).[2] However, in NMS there is an idiosyncratic reaction to several antipsychotic drugs or removal of exogenous dopaminergic agonists. It usually starts with muscular rigidity followed by hyperthermia and altered consciousness. Unlike the serotonin syndrome, 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 anaesthetics such as halothane and neuromuscular-blocking drugs such as succinylcholine).[8] In this case there was no recent exposure to antipsychotic drugs or anaesthetic drugs. The cases of serotonin syndrome have been reported with sertraline, trazodone and tramadol abuse.[9] This case report highlights that tramadol is a substrate of CYP 2D6 and fluoxetine an inhibitor of CYP 450 enzymes 2C9, 2C19, 2D6 and 3A4 which impair enzyme 2D6's ability to efficiently metabolize the tramadol and results in a pharmacodynamic synergy between tramadol's serotonergic blockades with fluoxetine a selective serotonin reuptake inhibitor (SSRI), leading to serotonin syndrome. Hence, it is vital that clinicians should be aware of the potential of serotonin syndrome when psychotropic and non-psychotropic

agents (e.g. Opioids) are co-administered to certain patients, such as those with both depression and pain.[10]

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