

CASE SERIES OF SEROTONIN SYNDROME CAUSED BY THE USE OF MULTIPLE ANTIPSYCHOTICSStephy Rachel Thomas^{*1}, Vandana Mohan¹, Dr. S. K. Mathew² and Dr. Joseph John³¹Pharm D Intern, Nazareth College of Pharmacy, Othera, Thiruvalla.²H.O.D, Department of General Medicine, Believers Church Medical College Hospital, Thiruvalla.³Assistant Professor, Department of General Medicine, Believers Church Medical College Hospital, Thiruvalla.***Corresponding Author: Stephy Rachel Thomas**

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Article Received on 21/12/2022

Article Revised on 11/01/2023

Article Accepted on 31/01/2023

ABSTRACT

Serotonin syndrome (SS) is a life-threatening condition resulting from increased serotonergic activity in the central nervous system. This can be a consequence of the use of therapeutic drugs, interactions between drugs or recreational drugs, or deliberate overdose. This literature is a case series of serotonin syndrome caused by the use of multiple antipsychotics.

KEYWORDS: Serotonin Syndrome, Antipsychotics, Cyproheptadine.**INTRODUCTION**

Serotonin syndrome, also known as serotonin toxicity, is a life-threatening condition resulting from increased serotonergic activity in the central nervous system. Symptoms can range from mild to fatal and classically includes altered mental status, autonomic dysfunction, and neuromuscular excitation.^[1]

Drug classes implicated include anti-migraine agents-triptans (e.g., Sumatriptan), antidepressants e.g. selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], buspirone, tricyclic antidepressants [TCAs], monoamine oxidase inhibitors [MAOIs], antipsychotics, anticonvulsants; antiparkinsonian agents, analgesics (e.g., meperidine, tramadol); OTC products (e.g., cough and cold medication containing dextromethorphan), herbal products (e.g., St. John's wort) and the antibiotic linezolid. Drugs that stimulate serotonin receptors include buspirone, dihydroergotamine, lithium, lysergic acid diethylamide (LSD), and metoclopramide.^[2] Mild SS episodes have been reported when St. John's wort or triptans have been used concurrently with SSRIs, SNRIs, or tricyclic antidepressants (e.g., amitriptyline). More severe SS episodes have been reported with the use of an MAOI with other serotonergic drugs (e.g., SSRIs, SNRIs).

Stimulation of the postsynaptic 5-hydroxytryptamine receptor 1A (5-HT_{1A}) and 5-hydroxytryptamine receptor 2A (5-HT_{2A}) receptors are involved in serotonin syndrome.

Several criteria exist for making the diagnosis: Sternbach, Radomski, and Hunter, but the Hunter criteria are generally accepted as the most accurate. Hunter's Criteria include:

- History of exposure to a serotonergic drug plus one or more of the following
- Spontaneous clonus
- Inducible clonus with agitation and diaphoresis
- Ocular clonus with agitation and diaphoresis
- Tremor and hyperreflexia
- Hypertonia
- Temperature over 38 degrees Celsius with ocular or inducible clonus.^[5]

No laboratory test confirms the diagnosis, but patients may have leukocytosis, elevated CPK, and decreased serum bicarbonate concentration. Patients may develop labile blood pressure, heart rate and cardiac dysrhythmias, disseminated intravascular coagulation, rhabdomyolysis, renal failure, metabolic acidosis, myoglobinuria, and respiratory failure.^[1]

Management consists of immediate termination of serotonergic agents, hydration, and supportive care to manage blood pressure, hyperpyrexia, and respiratory and cardiac complications. Sedation is best facilitated with benzodiazepines. Refractory cases may respond to the antidote, cyproheptadine.^[1]

We report two cases of the serotonin syndrome, treated with cyproheptadine, a 5-hydroxytryptamine receptor (5-HT) blocking agent with additional non-specific serotonin receptor blockade effects.

CASE REPORT 1

A 66-year-old male patient with a medical history of psychiatric illness managed with Olanzapine and Risperidone presented to the Emergency Department (ED) with visual hallucinations, altered sensorium, and increased irrelevant talks for two hours, following the addition of Gabapentin+Nortriptyline on account of worsening paresthesia which had been added to the treatment regimen a few days ago. He had a medical history of Parkinson's disease treated with Levodopa 100 mg + Carbidopa 25 mg, Type 2 Diabetes Mellitus managed with insulin and oral antidiabetic drugs (OADs)-Metformin 500 mg, and Hypothyroidism, for which he was on Thyronorm 75 mcg. On initial assessment, the patient was afebrile, and conscious but noted to be diaphoretic, restless, agitated, and confused. A physical examination of the patient revealed a heart rate of 116 beats/min, blood pressure of 150/90 mmHg and respiratory rate was 18/min.

Table 1.1: Biochemical Parameters.

Serum Creatinine	1.29 mg/dl
Total counts	8300/ μ L
Hemoglobin	11.0g/dl
C-Reactive Protein	17.8mg/L
Creatine kinase	96.5U/L.

Table 1.2- Arterial Blood Gas.

pH	7.277
pO ₂	24.1mmHg
pCO ₂	42.7mmHg
cLac	2.0mmol/L
cHCO ₃	16.2mmol/L

The limbs were generally rigid and he exhibited tremors and spontaneous, inducible clonus in the right hand. MRI brain along with a CSF examination was performed to rule out meningoencephalitis. Following the presence of spontaneous and inducible clonus with agitation, diaphoresis, and a history of concurrently using three serotonergic medications, a diagnosis of serotonin syndrome was suspected. The causal drugs were discontinued and intravenous fluid, thiamine injection, sedatives, and antibiotics were given along with the antidote cyproheptadine (Histamine-1 receptor antagonist). Cyproheptadine was started because of autonomic dysfunction suspecting serotonin syndrome. Clinical features of serotonin toxicity significantly improved after initiating cyproheptadine 8 mg, followed by 4 mg every 6 hours.

CASE REPORT 2

A 60-year-old male patient presented with complaints of acute abdominal pain and distension, and altered sensorium for a few days. The medical history showed psychosis, for which he was on Trifluoperazine+Trihexyphenidyl, Lithium, Risperidone, Thioridazine, and Clozapine. Recently he was treated at a nearby hospital for personality changes and insomnia and treated with Desvenlafaxine, after which he developed altered

sensorium. On initial assessment, the patient was afebrile, and conscious but noted to be diaphoretic, restless, and agitated. A physical examination of the patient revealed a heart rate of 107 beats/min, and blood pressure of 160/100mmHg.

Table 2.1- Biochemical Parameters.

Serum Creatinine	1.19 mg/dl
Total counts	11800/ μ L
Hemoglobin	14.1 g/dl
C-Reactive Protein	132.4 mg/L
Creatine kinase	98.7 U/L.

Table 2.2- Arterial Blood Gas

pH	7.402
pO ₂	34.1mmHg
pCO ₂	42.2mmHg
cLac	1.5mmol/L
cHCO ₃	19.3mmol/L

ECG of the patient showed sinus tachycardia and he started having repeated fever spikes. He was treated with a course of intravenous antibiotics-Piperacillin+Tazobactam 4.5g thrice daily. Other medications administered are Pantoprazole infusion because of aspiration pneumonia, nebulization with steroids and bronchodilators, antihypertensives, and other supportive medications. CT brain was taken because of persistent drowsiness and it showed sclerosis of mastoid air cells and calcific foci in the scalp and face. Based on features like diaphoresis, restlessness, agitation, elevated blood pressure, heart rate, and tachycardia, and also owing to the use of multiple antipsychotics, he was diagnosed as a case of probable serotonin syndrome. The causal drugs were discontinued and he was started with cyproheptadine 8 mg followed by 2 mg every 4 hours along with other supportive treatments. The patient improved and got discharged from the hospital 36 hours post-treatment.

DISCUSSION

Serotonin syndrome is a rare but potentially fatal interaction that has been precipitated by the combination of two or more drugs that enhance serotonin transmission, but it can occur after initiation of a single serotonergic drug or increasing the dose of a serotonergic drug in individuals who are particularly sensitive to serotonin.^[1] When patients take two or more antidepressants from different pharmacologic classes, drug-drug interactions may occur which may lead to potentially severe serotonin toxicity or SS.^[4]

SS may occur when central and peripheral serotonin receptors are overstimulated through the action of antidepressant medications or drugs of abuse. Both drug factors and patient factors can contribute to the toxicity of SSRIs in some individuals.^[5]

The cells of the raphe nuclei located in the midline of the brainstem are the source of neuronal 5-HT in the CNS. In the central nervous system, serotonin modulates attention, behavior, and thermoregulation. In the peripheral nervous system, serotonin is responsible for regulating gastrointestinal motility, vasoconstriction, bronchoconstriction, etc.^[6]

Mechanisms of serotonin syndrome are: (1) increased levels of L- tryptophan will lead to increased levels of endogenous 5-HT, a step catalyzed by the enzyme tryptophan hydroxylase 2 (TPH2). (2) Increased presynaptic concentrations of 5-HT due to inhibition of serotonin metabolism by MAOIs.^[6]

The diagnosis can be made in patients with a detailed history and thorough physical and neurologic examinations. Serotonin syndrome occurs several days to one week after the addition of a new serotonergic drug. Unless recognized and treated on time, serotonin syndrome has the potential to cause seizures, shock, and even death.

In the first case, the patient had several features suggestive of serotonin syndrome namely spontaneous and inducible clonus with agitation and diaphoresis, confusion, and low bicarbonate levels. The concomitant use of serotonergic agents (Olanzapine, Risperidone) and the addition of Gabapentin+Nortriptyline precipitated Serotonin syndrome in this patient. All his symptoms subsided upon discontinuation of serotonergic agents and the addition of serotonin antagonist, Cyproheptadine, and supportive measures.

The second patient had features of altered sensorium, confusion, tachycardia, and repeated fever spikes. Multiple antipsychotic drugs like Lithium, Thioridazine, Risperidone, and Clozapine probably triggered serotonin syndrome in this patient. Discontinuation of these antipsychotics and the addition of supportive measures and Cyproheptadine, a serotonin antagonist yielded improvement in patient status.

As these cases illustrate, serotonin syndrome can be caused by combinations of multiple drugs like antidepressants, atypical antipsychotics, SNRI, etc.

CONCLUSION

Serotonin syndrome is a life-threatening drug reaction that occurs by the overdose of one serotonergic drug or a combination of two or more medicines that affect the body's level of serotonin.

These cases highlight the incidence of serotonin syndrome following the use of multiple serotonergic agents, drawing attention to the need for all healthcare professionals to be on the lookout for potential cases of serotonin syndrome and be well-informed regarding the drugs and drug combinations with the potential to cause and precipitate serotonin syndrome.

ACKNOWLEDGEMENT

The authors would like to thank the Department of General Medicine, Believers Church Medical College Hospital, Thiruvalla, and Department of Pharmacy Practice, Nazareth College of Pharmacy, Othara for helping in reporting these case reports on Serotonin Syndrome.

CONFLICTS OF INTEREST

There are no conflicts of interest.

ABBREVIATIONS

CSF- Cerebrospinal fluid
 CT-Computed Tomography
 CPK- Creatine Phosphokinase
 CNS- Central Nervous System
 ECG- Electrocardiogram
 5-HT1A- 5-Hydroxytryptamine receptor 1A
 5-HT2A- 5-Hydroxytryptamine receptor 2A
 LSD- Lysergic Acid Diethylamide
 MAOIs- Monoamine oxidase inhibitors
 MRI-Magnetic Resonance Imaging
 SSRI- Selective Serotonin Reuptake inhibitors
 SNRI-Serotonin Norepinephrine Reuptake Inhibitors
 OADs-Oral Antidiabetic Drugs
 TCAs-Tricyclic Antidepressants
 TPH2- Tryptophan Hydroxylase 2

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