A 70-Year-Old Woman Presenting with Confusion and Muscle Spasms Due to Serotonin Syndrome Associated with Paroxetine and Quetiapine Treatment

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Patient: Female, 70-year-old
Final Diagnosis: Serotonin syndrome
Symptoms: Altered mental status • fever • tremor
Medication:
Clinical Procedure: Lumbar puncture
Specialty: Toxicology

Objective: Unusual clinical course
Background: Serotonin toxicity, often referred to as ‘serotonin syndrome,’ is a drug-induced condition due to excess serotonin released from brain synapses, resulting in symptoms that may be autonomic, neuromuscular, and/or cognitive in nature. Most cases involve more than 1 of the following drug regimens: monoamine oxidase inhibitors (MAOIs), serotonin releasers, selective serotonin reuptake inhibitors (SSRIs), or serotonin-norepinephrine reuptake inhibitors (SNRIs). This report is of a 70-year-old woman who presented with confusion and muscle spasms due to serotonin toxicity associated with paroxetine and quetiapine treatment.

Case Report: An elderly woman with dementia presented to the Emergency Department with fever, altered mental status, labile blood pressures, and inducible clonus. No known medication dosage increases had been made, nor had any new serotonergic agents been added to the patient’s drug regimen. She underwent a thorough workup in the Emergency Department and later during her hospitalization. A presumptive diagnosis of serotonin toxicity was made early on during her stay, with the etiology attributed to use of paroxetine and quetiapine. Clinical improvement was observed after benzodiazepine administration, discontinuation of offending agents, and a brief cyproheptadine course. The patient survived her hospital stay and was ultimately discharged to hospice care with a return to her baseline level of functioning.

Conclusions: Diagnosing serotonin toxicity requires a high degree of clinical suspicion and can occur in the absence of increased dosage of existing, or initiation of new, serotonergic agents.

Keywords: Paroxetine • Quetiapine Fumarate • Serotonin • Serotonin Syndrome

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/938268
A 70-year-old woman was brought in by her husband due to 2 weeks of progressive behavior changes, gait disturbance, and generalized weakness that had worsened over the previous 3 days. Her home health aide had noted increased lethargy and a diffuse tremor during the week prior to presentation. She was minimally verbal at baseline but could typically perform activities of daily living without difficulty. Her husband and aide denied any recent illness, fever, trauma, shortness of breath, urinary symptoms, diarrhea, or skin changes.

Her past medical history was significant for hypertension, hyperlipidemia, depression, and dementia, and her past surgical history was significant for thyroidectomy. Her family history was non-contributory, and she had no known drug allergies. Her home medications included lisinopril, quetiapine, paroxetine, and atorvastatin. Her vital signs were: rectal temperature 39.3°C; blood pressure 109/80 mm of mercury (mmHg); heart rate 104 beats per minute; respiratory rate 25 breaths per minute; and oxygen saturation 93% on room air. A physical examination was notable for a patient in moderate distress who exhibited a resting tremor in all 4 extremities. Her neck was contracted to the left but had full passive range of motion. Her pupils were equal, round, and reactive to light and accommodation, and extraocular movements were intact. Hyperreflexia and 6 beats of inducible clonus were noted. The results of cardiopulmonary, abdominal, and skin examinations were all unremarkable. Chemistries, blood cultures, and urine studies were collected, and the patient was given acetylmethophen, vancomycin, ceftriaxone, acyclovir, ampicillin, diazepam, and 2 L of lactated Ringer’s solution.

Laboratory findings were significant for blood urea nitrogen (BUN) 53 mg per dL (mg/dL, reference range 7-20 mg/dL), creatinine 2.1 mg/dL (reference range 0.6-1.1 mg/dL), aspartate aminotransferase (AST) 89 international units per liter (IU/L, reference range 5-34 IU/L), alanine aminotransferase (ALT) 96 IU/L (reference range 0-37 IU/L), alkaline phosphatase 156 IU/L (reference range 40-150 IU/L), creatine kinase 1466 units per liter (IU/L, reference range 29-168 IU/L), lactate dehydrogenase 421 IU/L (reference range 125-220 IU/L), troponin 1 0.046 nanograms per milliliter (ng/mL, reference range <0.04 ng/mL), and white blood cell count 19 700 cells per micro-liter (cells/μL, reference range 4000-10 000 cells/μL). Initial venous blood gas results were: pH 7.47 (reference range 7.3-7.4), pCO2 31 mmHg (reference range 40-50 mmHg), pHCO3 22 millimoles per liter (mmol/L, reference range 21-28 mmol/L), and lactate 1.7 mmol/L (reference range 0-1.9 mmol/L). The hematocrit/hematocrit, platelets, antinuclear antibody (ANA), complement 3 and 4 levels (C3, C4), procalcitonin, vitamin B12, and thyroid function were all within normal limits. Tests for human immunodeficiency virus (HIV), syphilis, and coronavirus disease-19 (COVID-19) were non-reactive. Alcohol, salicylates, and acetylmethophen were not detected. Lumbar puncture showed normal opening pressure and cerebrospinal fluid chemistries, as well as a negative meningitis-encephalitis polymerase chain reaction panel for all tested pathogens (Escherichia coli, Haemophilus influenza, Streptococcus agalactiae and pneumonae, Cytomegalovirus, Enterovirus, Herpes simplex virus, Human herpes virus 6, Human parechovirus, Varicella zoster virus, and Cryptococcus neoformans). Blood, urine, and cerebrospinal cultures yielded no growth.

Electrocardiography showed sinus tachycardia with narrow QRS complexes, normal QTc intervals, and no ischemic changes. A chest X-ray revealed no acute pulmonary pathology. Computed tomography (CT) of the head was negative for acute intracranial pathology. The patient was admitted to the Medicine Department for encephalopathy secondary to a suspected toxidrome and metabolic derangements.

Cyproheptadine was given every 2 h, with improvement in clonus. The elevations in white blood cell count, transaminases, troponin, creatinine, and creatine kinase all resolved. Video electroencephalography (EEG) was performed and showed mild-to-moderate generalized slowing as well as focal slowing in the right temporal lobes with sharp waves that were non-epileptiform; these findings were consistent with non-specific,
diffuse cerebral dysfunction and focal dysfunction in the right temporal region. Vancomycin, ceftriaxone, ampicillin, and acyclovir were discontinued. A gradual return to baseline followed and the patient was discharged to hospice care.

Discussion

Serotonin toxicity can present similarly to many more common pathologies that are observed in the emergency department. It should be considered, assessed for, and diagnosed relatively quickly to be properly treated. While there is no criterion standard test for diagnosis of serotonin toxicity, toxicologists can help identify serotonin-toxic patients. Platelet-bound serotonin assays exist for diagnostic purposes but are not functionally useful in practice [8]. The Hunter Criteria are widely recognized in aiding diagnosis of serotonin toxicity and were found to be highly sensitive (84%) and specific (97%) [3]. They consist of ingestion of a known serotonergic agent along with at least 1 of the following: (1) spontaneous clonus, (2) inducible clonus AND diaphoresis OR agitation, (3) oculomotor clonus AND diaphoresis OR agitation, (4) tremor AND hyperreflexia, (5) hypertension AND temperature greater than 38°C AND ocular OR inducible clonus [9]. The presentation of this patient was consistent with serotonin toxicity given the ingestion of a serotonergic agent along with elevated temperature, tachycardia, hypertension, and inducible clonus. In addition, the diagnosis was supported by improvement in the patient’s status after benzodiazepine and cyproheptadine administration. The history-taking was limited by the patient’s mental status, and it was crucial to perform a thorough physical examination to arrive at this uncommon clinical diagnosis. This case also reinforces the importance of maintaining a broad differential diagnosis in elderly patients presenting with altered mental status. Finally, 5-HT toxicity should remain on the differential diagnosis even in the absence of an obvious trigger such as new serotonergic agents or increased dosing of already-prescribed serotonin agonists.

Chiew et al (2021) performed an extensive review of the literature regarding cases of serotonin toxicity and analyzed the 4 proposed criteria: Sternbach, Serotonin Syndrome Scale, Radomski, and Hunter. The Serotonin Syndrome Scale has limited applicability in that it is only utilized in patients taking a serotonergic agent but has not been validated for those with serotonin toxicity. The other 3 criteria are more targeted toward serotonin-toxic patients but have not been thoroughly refined or validated. An examination of case fatalities reveals the shortcomings of these diagnostic criteria. Twelve out of 55 (22%) of cases reviewed were unlikely to be serotonin toxicity. The Sternbach and Radomski criteria were met by 25 patients (45%); 20 patients (36%) did not have sufficient data reported and 10 patients (18%) met an exclusion criterion. Few patients had sufficient data to determine whether Hunter Criteria were met; only 13 patients (24%) were listed as meeting the criteria and the remaining 42 patients (76%) had insufficient data [10].

Our patient’s Emergency Department course was notable for episodes of hypotension, with systolic blood pressures as low as 60 mmHg. 5-HT can cause both hypotenison (5-HT1A agonism) and hypertension (5-HT3 agonism) [11]. Prior case reports have suggested increasing doses of cyproheptadine or propofol administration for severe hypertension [12]. Few reports of sustained hypotension exist, and we therefore suggest continued consultation with toxicology specialists, supportive care with vasopressors as needed, and investigating if alternative physiologic processes are present.

There are numerous drugs with potential to contribute to serotonin toxicity. They include, but are not limited to, monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), opiates, antitussive agents, antibiotics, weight-reducing agents, antiemetics, antimiagrine agents, and herbal products [2]. Serotonin toxicity can be caused by increasing doses of these medications, the addition of new serotonergic agents, or an interaction between agents. Toxicity has been reported after just a single therapeutic dose of an SSRI [13]. Several case reports describe presentations consistent with serotonin toxicity in patients receiving an antipsychotic agent together with a serotonin modulator [14-18]. The patient’s home medications included paroxetine, an SSRI, as well as quetiapine, an atypical antipsychotic. Atypical antipsychotics are known to be disinhibitory at serotonin receptors; prior case reports suggest that quetiapine’s 5-HT2A antagonism can paradoxically increase sensitivity to other 5-HT receptors, thereby making an individual more prone to serotonin toxicity [14,15].

Management of serotonin toxicity includes removal of offending agents, administration of 5-HT antagonists, controlling agitation, and aggressive temperature management [12]. Agitation should be addressed with gamma-aminobutyric acid (GABA) agonists such as benzodiazepines. Death is often secondary to hyperthermia, and temperature control is critical. Severe toxicity with persistent, intractable, and excessive clonus warrants consideration of neuromuscular blockade and establishment of a definitive airway. Cyproheptadine should be considered for unstable and symptomatic patients [18]; it is an antihistamine with non-specific serotonin antagonism at the 5-HT1A and 5-HT2A receptors [19,20]. One practical administration limitation of cyproheptadine is that it is an oral medication and must be given via an oral or nasogastric tube in endotracheally intubated patients. It is difficult to find well-performed, randomized, case/control trials that demonstrate clear improvement after administration of cyproheptadine. However, there are multiple
case reports supporting its use that report improvement after cyproheptadine administration. Initial dosing suggestions are variable and can range from 8 mg to 16 mg orally or via nasogastric tube, repeated hourly, every 2 h, or every 4 h as needed to titrate to muscle relaxation, symptomatic improvement, and additional desired clinical responses [18].

References:

1. Prakash S, Rathore C, Rana K, Patel H. Antiepileptic drugs and serotonin syndrome – a systematic review of case series and case reports. Seizure. 2021;91:117-31
2. Boyer EW, Shannon M. The serotonin syndrome. N Engl J Med. 2005;352:1112-20
3. Dunkley EJ, Isbister GK, Sibbritt D, et al. The Hunter Serotonin Toxicity criteria: Simple and accurate diagnostic decision rules for serotonin toxicity. QJM. 2003;96:635-42
4. Ishida T, Uchida H, Kaneko S, et al. Life-threatening serotonin syndrome precipitated by discontinuation of serotonin-dopamine antagonist in the presence of serotonergic agents: A case report. Clin Neuropharmacol. 2020;43:81-83
5. Gould M, Harrison WD, Cahill-Kearns A, Barton G. Fever in a patient with osteomyelitis: The diagnosis could be serotonin syndrome. BMI Case Rep. 2021;14:e239152
6. Talarico G, Tosto G, Pietracupa S, et al. Serotonin toxicity: A short review of the literature and two case reports involving citalopram. Neurol Sci. 2011;32:507-9
7. Dursun SM, Mathew VM, Reveley MA. Toxic serotonin syndrome after fluoxetine plus carbamazepine. Lancet. 1993;342:442-43
8. Brenner B, Harney JT, Ahmed BA, et al. Plasma serotonin levels and the platelet serotonin transporter. J Neurochem. 2007;101(2):206-15. Erratum in: J Neurochem. 2008;107(1):302
9. Prakash S, Rathore C, Rana K, Prakash A. Fatal serotonin syndrome: A systematic review of 56 cases in the literature. Clin Toxicol (Phil). 2021;59:89-100
10. Chiew AL, Buckley NA. The serotonin toxidrome: Shortfalls of current diagnostic criteria for related syndromes. Clin Toxicol (Phil). 2022;60(2):143-58
11. Fraer M, Kilic F. Serotonin: A different player in hypertension-associated thrombosis. Hypertension. 2015;65:942-48
12. Ott M, Mannchen JK, Jamshidi F, Wemeke U. Management of severe arterial hypertension associated with serotonin syndrome: A case report analysis based on systematic review techniques. Ther Adv Psychopharmacol. 2019;9:2045125318818814
13. Gill M, LoVecchio F, Selden B. Serotonin syndrome in a child after a single dose of fluvoxamine. Ann Emerg Med. 1999;33:457-59
14. Kohen I, Gordon M, Manu P. Serotonin syndrome in elderly patients treated for psychotic depression with atypical antipsychotics and antidepressants: Two case reports. CNS Spectr. 2007;12:596-598
15. Marlowe K, Schirgel D. Quetiapine and citalopram: Aetiological significances in serotonin syndrome. N Z Med J. 2006;119:U2058
16. Stork, CM. Serotonin reuptake inhibitors and atypical antidepressants. In: Nelson LS, Howland M, Lewin NA, et al (eds.). Goldfrank's toxicologic emergencies. 11th ed. China: McGraw Hill; 2019;1054-64
17. Graudins A, Stearman A, Chan B. Treatment of the serotonin syndrome with cyproheptadine. J Emerg Med. 1998;16(4):615-19
18. Lappin RI, Auchincloss EL. Treatment of the serotonin syndrome with cyproheptadine. N Engl J Med. 1994;331:1021-22

Conclusions

Serotonin toxicity requires a high degree of clinical suspicion and can occur even in the absence of increased dosage of existing medications or initiation of new serotonergic agents.

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