

Serotonin syndrome after taking citalopram

CASE REPORT

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INTRODUCTION

Serotonin syndrome is a potentially life-threatening condition associated with increased serotonergic activity in the central nervous system. It has been observed in all age groups including newborns and the elderly.¹ It is characterised by a triad of mental status changes, autonomic hyperactivity and neuromuscular abnormalities. It is seen with therapeutic medication use, inadvertent interactions between drugs, as well as intentional self-poisoning.¹

Citalopram is an antidepressant targeting the serotonin pathway (a selective serotonin reuptake inhibitor). Indications for citalopram use include treatment of depression, anxiety neurosis, panic disorder and obsessive-compulsive disorder. It is well tolerated, with mild side-effects including a dry mouth, gastrointestinal disturbance and dizziness. It is rarely associated with serotonin syndrome.

CASE REPORT

In November 2008, an 81-year-old Chinese woman presented to Queen Mary Hospital after a fall. She had hypertension, type-II diabetes and anxiety neurosis managed with regular medical and psychiatric follow-up. She reported experiencing dizziness, poor postural balance and gait instability, but no loss of consciousness, before her fall. This was her second fall in recent years.

Prior to admission, she was taking lisinopril 10 mg daily, nifedipine (slow-release) 20 mg twice a day for her hypertension, and gliclazide 120 mg twice a day for her diabetes. Her vital signs were stable on admission, with a blood pressure of 130/75 mm Hg, a pulse rate of 85/min. Haemostix performed on

admission gave a reading of 6.1. When her postural blood pressure was checked, the systolic reading showed 7 to 10 mm Hg drop, so the nifedipine was replaced with amlodipine 2.5 mg daily.

She had been diagnosed with anxiety-depression in September 2002 and was given flupentixol (a typical antipsychotic) 0.5 mg daily, malitracen (a tricyclic antidepressant) 10 mg daily, benzhexol (an anti-muscarinic) 2 mg twice a day and lorazepam (a benzodiazepine) 2 mg nocte. She developed extrapyramidal side-effects, including tremors and limb rigidity, which contributed to her increased risk of falling.

After consultation with our psychiatry team, her psychiatric medications were ceased and switched to citalopram 10 mg daily and diazepam 1 mg nocte. However, she developed a high fever, registering a temperature of 40°C on the second day after starting citalopram. She became very drowsy and confused. Her blood pressure increased to 180/100 mm Hg, and electrocardiography showed sinus tachycardia with a heart rate reaching 130/min. A neurological examination found no neck stiffness, focal neurological deficits or spontaneous clonus. Nonetheless, she demonstrated limb rigidity and her deep tendon reflexes were brisk bilaterally.

The citalopram was stopped immediately and she was given intravenous fluids. A full septic workup (including blood, urine and sputum cultures) was performed, all of which grew nothing. Blood tests revealed a raised white cell count of $11.7 \times 10^9/L$ (normal range, $4.4-10.1 \times 10^9/L$), a raised creatine phosphokinase level of 486 U/L (normal range, 40-161 U/L), and a mildly raised lactate dehydrogenase level of 53 U/L (normal range, 15-37 U/L). Computed

TABLE
Distinguishing features of serotonin syndrome and neuroleptic malignant syndrome

Features	Serotonin syndrome	Neuroleptic malignant syndrome
Onset	Within 24 hours	Days to weeks
Causative agents	Serotonergic agents	Dopamine antagonists
Neurological findings	Hyperactivity including tremors, clonus, hyperreflexia	Hypoactivity including rigidity and bradyreflexia
Treatment strategy	Benzodiazepine, cyproheptadine	Bromocriptine
Resolution	Within 24 hours	Days to weeks (average 9 days)

tomography of her brain revealed age-related atrophic changes only.

The diagnosis of serotonin syndrome related to the newly introduced citalopram was confirmed. The intravenous fluid supplement was maintained, her vital signs were closely monitored, and she was sedated with diazepam 2 mg daily. Her temperature returned to normal within 24 hours of stopping the citalopram. She made an uneventful recovery and was discharged home after a short rehabilitation exercise course in a convalescent unit.

DISCUSSION

The diagnosis of serotonin syndrome is made solely on clinical grounds. Therefore, a detailed history and thorough physical examination are essential.² In particular, a temporal relationship with starting or a change in the dosage of a serotonergic agent is of the utmost importance.

Common clinical features of serotonin syndrome include mental status fluctuation, autonomic hyperactivity and neuromuscular changes. Patients may startle easily, become drowsy, agitated and restless.³ Autonomic hyperactivity can manifest as hyperthermia, tachycardia and fluctuations in blood pressure.⁴ Neuromuscular hyperactivity (including rigidity, hyperreflexia and clonus) is common.⁴ Special attention should be paid when performing a neurological examination. Slow, continuous horizontal eye movements (ocular clonus) are typically seen in serotonin syndrome.¹ Tremors, akathisia, deep tendon hyperreflexia, bilateral up-going Babinski signs and muscle clonus are also often seen. Neuromuscular signs are usually more pronounced in the lower extremities.⁴

Different sets of diagnostic criteria have been developed to define serotonin syndrome. The

most accurate—Hunter toxicity criteria—has 84% sensitivity and 97% specificity,⁵ when compared with the gold standard diagnosis by a toxicologist. To fulfil the Hunter criteria, a patient must have taken a serotonergic agent plus show one of the following: (1) spontaneous clonus, (2) inducible clonus plus agitation or diaphoresis, (3) ocular clonus plus agitation or diaphoresis, (4) tremor and hyperreflexia, (5) hypertonia and a temperature above 38°C plus ocular clonus or inducible clonus.

Serotonin syndrome is often misdiagnosed as neuroleptic malignant syndrome (NMS),⁶ but history, physical examination findings and the clinical course make it possible to distinguish between the 2 (TABLE). Serotonin syndrome develops during the 24 hours after starting or escalating the dosage of serotonergic agents, whereas NMS develops over days to weeks.⁴ Serotonin syndrome is characterised by neuromuscular hyperactivity, which includes tremor, hyperreflexia and myoclonus, whereas patients with NMS show sluggish responses, including bradyreflexia and rigidity.⁴ Moreover, NMS requires an average of 9 days to resolve, compared with less than 24 hours in serotonin syndrome.⁶ Our patient had been on flupenthixol for 6 years, making NMS much less likely because NMS usually develops within days to weeks of initiating new antipsychotic drugs.

Laboratory tests are usually non-specific, showing a leucocytosis, elevated creatine phosphokinase levels, elevated liver transaminases and metabolic acidosis in severe cases,⁴ features seen in both serotonin syndrome and NMS. It should be noted that there is no correlation between serum serotonin levels and clinical findings,⁴ and no specific laboratory test able to confirm the diagnosis, making a thorough history and physical examination crucial. Other differential diagnoses for serotonin syndrome include malignant hyperthermia, central nervous

system infection, and delirium tremens seen in alcohol and benzodiazepine withdrawal.

Management of serotonin syndrome requires quick recognition and prompt withdrawal of all serotonergic agents. Supportive care should be given, aiming at normalising the vital signs.¹ In more severe cases, sedation with benzodiazepines and the administration of serotonin antagonists (cyproheptadine) may be required.⁷ Hyperthermic and critically ill patients occasionally require paralysis and endotracheal intubation. Cyproheptadine is a histamine-1 receptor antagonist with non-specific 5-HT_{1A} and 5-HT_{2A} antagonistic properties. It has been reported to be useful for managing serotonin syndrome.⁷⁻⁹ Cyproheptadine may lead to sedation and produce transient hypotension due to the reversal of serotonin-mediated increases in vascular tone, but these side-effects are usually mild and subside with intravenous hydration.⁸

CONCLUSION

Greater use of anti-depressants targeting the serotonin pathway is making side-effects of these drugs more common. We describe a case of serotonin syndrome seen in an elderly woman after she was commenced on citalopram. Prompt recognition and

supportive care enabled the patient to make a good recovery. Serotonin syndrome has a broad spectrum of clinical severity, from mild cases of flushing and diaphoresis to critical cases requiring intubation and intensive care. Clinicians should be aware of this potentially life-threatening side-effect, and weigh the benefits and risks when selecting treatment and deciding whether to continue the causative agent.

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