CASE REPORT

Serotonin syndrome caused by drug to drug interaction between escitalopram and dextromethorphan

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SUMMARY

A 63-year-old woman with a history of long-standing depression, maintained on escitalopram, presented with altered mental status. Patient had recently been prescribed dextromethorphan-promethazine cough syrup 2 weeks prior for an upper respiratory tract infection. On admission, she was lethargic and obtunded and found to have inducible myoclonus on examination. The rest of her physical exam was unremarkable. Pertinent lab and imaging findings showed QTc prolongation on ECG, negative electroencephalogram and CT head findings, essentially normal blood tests and a negative toxicology screen. The patient was admitted to the step down unit for close observation; both escitalopram and the cough syrup were suspended and was supportively managed. Overnight the patient's mental status improved and the serial ECGs showed resolution of the prolonged QTc. Patient was discharged home without further complication.

BACKGROUND

Serotonin syndrome is an often unrecognised clinical condition that presents with spectrum of symptoms and signs.¹ Reportedly therapeutic doses of serotonergic medications alone rarely cause severe toxicity; overdoses often lead to mild to moderate toxicity.² Drug interactions that alter serotonin metabolism are often the causes leading to severe toxicity.² Once recognised, the main treatment is removal of the offending medications.^{1,2} Through a thorough history and physical exam, clinicians should be able to recognise the signs and symptoms of serotonin syndrome and quickly manage a patient accordingly.^{1,2} Clinicians need to be aware of potential drug interactions between prescription and over-the-counter medications that can provoke this syndrome. This case report aims to describe a clinical scenario of drug interactions, a selective serotonin reuptake inhibitor (SSRI) and medication readily available over the counter.

CASE PRESENTATION

A 63-year-old woman, presented to the emergency department (ED) with altered mental status. Approximately 1.5 hours prior to arrival, the patient was found unresponsive in bed by her husband, who had then called emergency medical services (EMS).

On further inquiry of the patient's husband, the patient had been sick over the past 2 weeks with cold-like symptoms, non-productive cough, chest discomfort but no fever or chills. The patient was maintained on long-standing escitalopram for her depression. She had consulted her primary care physician and was given cough syrup containing dextromethorphan-promethazine. After 5 days, there was reported loss of appetite, sleep talking and poor sleep. Two days prior to ED admission, there was note of possible auditory and visual hallucinations. Over 2 weeks, she progressively had cognitive decline, described as 'not her usual self' and acting slower than usual.

On arrival in the ED in the evening, she was briefly awake but restless with twitching of her upper extremities. Vital signs were blood pressure of 110/82, heart rate 85 bpm, respiratory rate 20 breaths per min with oxygen saturation 96% on 2L nasal cannula and temperature of 36.6°C. She received levetiracetam and lorazepam due to questionable seizure activity. Oral examination showed dry blood on the tongue, noted by the husband from probable tongue biting during sleep. Cardiovascular, respiratory and abdominal exams were unremarkable. Neurological exam showed intermittent upper extremity twitching, despite receiving lorazepam. Patient also had bilateral lower extremity myoclonus. By the following morning, her mental status had worsened; she was obtunded with only withdrawal to pain. She was placed on bilevel positive airway pressure (BiPAP) for increasing respiratory distress and brought to the step down unit for observation after all her medications were suspended.

Medical history was significant for depression, anxiety, hypertension and alcohol use with history of withdrawal seizure. She had been treated for alcohol detoxification and was on naltrexone intramuscular injection 1 month prior to admission. Patient had been sober and the husband denied any alcohol ingestion prior to admission. Her medications consisted of amlodipine 5 mg twice daily, labetalol 100 mg daily and escitalopram 10 mg daily. Husband denied any possible overdose of her medications, any recent changes in medications, except for the newly prescribed

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promethazine-dextromethorphan cough syrup, which was found to be appropriately consumed.

INVESTIGATIONS

Initial blood tests showed leucocytosis with white blood cell of 11.4 K/cmm and neutrophil of 80%. Electrolytes were within normal limits (sodium 142 mEq/L, potassium 4.0 mEq/L, chloride 100 mEq/L, calcium 9.5 mg/dL, phosphorus 4.1 mg/dL and magnesium 2.4 mg/dL) except for the bicarbonate 36 mEq/L. Blood glucose was 128 mg/dL. Her creatinine was normal but her blood urea nitrogen:creatinine ratio was greater than 20, consistent with dehydration given patient's recent history of decreased intake. Liver function tests were normal. Arterial blood gas showed compensated respiratory acidosis with pH of 7.39, pCO₂ of 47 mm Hg and pO₂ of 56 mm Hg. Urine toxicology was positive for benzodiazepines due to the lorazepam received in the ED. Ethanol level was less than 10 mg/dL and undetectable salicylate and acetaminophen levels. Urinalysis was negative for any infection. Troponin-I was negative.

An initial plain head CT did not show any acute bleed or mass. Chest X-ray showed no acute cardiopulmonary disease. ECG done on admission showed 1st degree atrioventricular block with QTc 724 ms. Prior ECGs had QTc of 512–535 ms.

DIFFERENTIAL DIAGNOSIS

The patient's initial working diagnosis was serotonin syndrome, QTc prolongation and a viral upper respiratory tract infection. Differential diagnosis at the time included possible postictal alcohol withdrawal seizure.

TREATMENT

Poison controlled was called for further recommendations; recommending cyproheptadine should the patient's condition worsen. She was admitted to the step down unit for close monitoring. Escitalopram and the cough syrup were suspended on admission. Patient was managed supportively; given intravenous fluids and kept nothing per mouth until her mental status improved. She was placed on BiPAP to maintain oxygen saturation. Electrolytes and ECG were closely monitored.

OUTCOME AND FOLLOW-UP

Overnight, the patient was stable and by morning she was more awake and alert. She no longer required BiPAP, was tolerating room air and was able to tolerate oral intake without problems. Chemistry panel remained normal and ECG improved to 522 ms, with subsequent QTcs from 450 to 480 ms. EEG did not show seizure activity. ECHO and nuclear stress testing were unremarkable. Patient had returned to baseline, told to discontinue her SSRI and was discharged home with follow-up with her primary care provider and psychiatrist.

DISCUSSION

Serotonin syndrome is often described as a clinical triad of autonomic hyperactivity, mental status changes and neuromuscular hyperexcitability.^{1–4} It was first noted in 1960s by Oates and Sjostrand and eventually further characterised in 1991 by Sternbach with the development of the Sternbach Criteria.^{5–6} Serotonin syndrome is caused by excessive levels in the central nervous system either by impairment of metabolism, impaired reuptake, increased serotonin release or increased serotonergic precursors.²

Clinically, serotonin syndrome has a broad range of presentations that often result in under diagnosis.^{1–4,7} Mild cases may

result from therapeutic doses, and the patient may or may not be symptomatic.^{1,2} Moderate cases present with more autonomic and neurological dysfunction. Severe cases generally presents with worsening vital signs, rigidity, hyperthermia and the potential for multiorgan failure.^{1,2,4} Treatment depends on the severity of the presentation. Mild cases are managed supportively; managing the symptoms and withdrawal of the offending medications.⁴ Moderate cases are managed similarly but monitored closely for hyperthermia. Severe cases require the prevention of hyperthermia and rigidity through sedation, paralysis, intubation and administration of serotonin antagonists, such as cyproheptadine.⁴

Other conditions with similar presentations are: anticholinergic toxidrome, neuroleptic malignant syndrome and malignant hyperthermia.^{2,4,7} Autonomic dysfunction, mental status changes and changes in muscular tone are common in these conditions.² Only serotonin syndrome presents with hyper-reflexia and clonus.²

Based on limited case report data, most cases of serotonin syndrome do not appear to be associated with therapeutic doses of a single medication but due to either overdose or medication interactions resulting in supratherapeutic levels of a single agent.^{2,6,8–10}

Dextromethorphan is a common drug found in many over-the-counter cough medications. There have been limited case reports citing interactions between dextromethorphan¹⁰ and SSRIs. Other reported interaction involved SSRIs and monoamine oxidase inhibitors, such as selegiline.³ Tricyclic antidepressants and opioids have reported cases of serotonin syndrome.^{7,11} Both dextromethorphan and the SSRI escitalopram are metabolised by CYP2D6, potentiating the serotonin reuptake effect.^{6,10}

Our patient was found with altered mental status but was awake and agitated in the ED prior to receiving lorazepam. On examination, she had intermittent arm twitching, sluggish papillary reaction and inducible clonus of the lower extremities. Despite the absence of fever and tachycardia, the presentation along with the history of escitalopram and dextromethorphan intake strongly suggests serotonin syndrome. Supporting this diagnosis was the ECG findings of QTc prolongation, a noted effect of SSRIs. The patient's quick recovery after removal of the offending medications further supports the diagnosis.

In conclusion, serotonin syndrome frequency and severity increases with drug interactions of medications such as SSRI and over-the-counter medications such as dextromethorphan. Review of medication interactions is important to prevent serotonin syndrome,¹² and recognition through examination and review of medications is key to preventing further complications.²

Learning points

- Recognise the symptoms and signs of serotonin syndrome.
- Understand the treatment of serotonin syndrome based on severity.
- Check for possible drug interactions between medications including over the counter drugs.

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