Case Report

Citalopram overdose and severe serotonin syndrome in an intermediate metabolizing patient

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Abstract

Introduction: Citalopram is a selective serotonin reuptake inhibitor used for treatment of depression. Metabolism is primarily through CYP3A4 and CYP2C19; activity of the latter can vary depending on genetics. Although rare after single agent exposure, large citalopram ingestions can lead to serotonin syndrome. We report a case of citalopram overdose in an intermediate CYP2C19 metabolizer complicated by severe serotonin syndrome.

Case details: A 25-year-old female presented after intentional citalopram overdose with seizures, tachycardia, persistent neuromuscular findings, and severe hyperthermia requiring aggressive sedation and cooling. Protracted symptoms required critical care services throughout a 14 day hospital stay despite traditional treatment of serotonin syndrome. Pharmacogenomic studies revealed intermediate CYP2C19 metabolism which reduces citalopram inactivation and may cause increased levels and toxicity.

Discussion: In the majority of serotonin syndrome cases, symptoms resolve rapidly after treatment initiation and discontinuation of the offending agents. Severe cases are typically associated with ingestion of multiple serotonergic agents. Our patient had severe toxicity after single agent ingestion. Pharmacogenetic testing identified abnormal CYP2C19 activity and previous cases have associated enzyme dysfunction and citalopram toxicity.

Conclusion: Citalopram overdose may be associated with severe serotonin syndrome and further investigation is warranted to understand the impact of enzyme genotype on toxicity.

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1. Introduction

Selective serotonin reuptake inhibitors (SSRIs) are commonly used to treat depression. In the last decade, the United States has seen a surge in antidepressant use and toxicity [1]. While serotonin syndrome presents along a spectrum of illness, severe serotonin syndrome can present as a life-threatening reaction and typically occurs after exposure to a combination of serotonergic medications [2]. We report a case of severe serotonin syndrome following citalopram overdose in a patient with intermediate CYP2C19 metabolism.

2. Case details

A 25-year-old female with history of depression presented to the emergency department 7 h after ingesting 760 mg citalopram in a suicide attempt. Upon presentation, she was noted to be anxious and tremulous with heart rate 162 beats/min, blood pressure 107/69 mmHg, respirations 18 breaths/min, and temperature 36.7 °C. She developed tonic-clonic seizure activity and was intubated for airway protection using midazolam and fentanyl for continuous sedation. She was given intravenous magnesium sulfate for QT prolongation. Initial labs were significant for leukocytosis (18.7 × 103/L), low bicarbonate (18 mmol/L), and elevated anion gap (17). Medical Toxicology was consulted and she was admitted to intensive care unit (ICU).

On ICU evaluation, she was hyperthermic (38.5 °C) with severe rigidity and difficulty eliciting clonus due to hypertonnia. Recommendations included discontinue fentanyl, titrate midazolam infusion to relaxed tone, and cyproheptadine 8 mg per nasogastric tube three times daily. Additionally, escalating doses of phenobarbital were recommended as needed for additional symptom control. Despite aggressive sedation and external cooling, there was persistent lower extremity rigidity with hyperreflexia, tremors, and clonus; temperature peaked on day two (40.2 °C) and creatine kinase peaked approximately 42 h post ingestion (7671 U/L). Temperature improved and remained below 38 °C on day three. Due to persistent neuromuscular findings, pentobarbital was started the evening of day three at 10 mg/kg over 1 h, then 5 mg/kg/h for three hours, and 1 mg/kg/h. Neuromuscular excitation was considerably improved the following morning; pentobarbital was gradually tapered and ultimately discontinued on day six. Despite normal neuromuscular exam documented on day five, fever returned and
antibiotics were administered for suspected aspiration pneumonia. The patient was extubated on day nine.

Comprehensive urine drug screening for 289 pharmaceutical and recreational drugs utilizing immunoassay and liquid chromatography-mass spectrometry identified only citalopram other than hospital-administered medications. The patient’s citalopram concentration (normal: 9–200 ng/mL) was 2900 ng/mL 7 h post ingestion, 730 ng/mL 53 h post ingestion, and 340 ng/mL 65 h post ingestion. Renal and hepatic function remained normal throughout hospitalization. Pharmacogenetic testing revealed intermediate CYP2C19 metabolism.

3. Discussion

We report a case of severe serotonin syndrome following citalopram ingestion in an intermediate CYP2C19 metabolizer. Previous experience with citalopram overdose suggests symptom severity and duration in our patient was atypical. Literature reports mild symptoms at doses <600 mg with doses over 1900 mg resulting in ECG changes and seizures in all patients [1]. Additionally, symptoms typically improve after 24 h of treatment [2].

Serotonin syndrome is described as a triad of symptoms including mental status changes, autonomic hyperactivity, and neuromuscular abnormalities. Symptoms may persist due to a variety of reasons including ingestion of drugs with long elimination half-lives, active metabolites, or long duration of action. Management includes discontinuation of serotonergic agents and supportive care, but treatment intensity depends on symptom severity [2]. Although more likely with multiple serotonergic co-ingestions, a fatal case of serotonin syndrome was described in a 35-year-old female after citalopram overdose (concentration 7300 ng/mL) with no known co-ingestions. She presented with seizure, cyanosis, and cardiac arrest reportedly experiencing evidence of serotonin syndrome such as fever above 38 °C and rigidity on exam prior to death [3].

Pharmacogenetic testing determined that our patient was an intermediate CYP2C19 metabolizer, the primary enzyme responsible for citalopram metabolism. This polymorphism causes reduced citalopram inactivation which may increase concentrations and toxicity. Despite correlations between CYP2C19 polymorphisms and citalopram serum concentrations, there are currently no therapy changes recommended for intermediate metabolizers [4,5]. Available reports describe three patients with citalopram toxicity likely related to altered CYP2C19 metabolism. Two patients received therapeutic doses of fluconazole (CYP2C19 inhibitor) with citalopram and developed symptoms of citalopram toxicity including seizures in one patient and delirium in both [6]. A 46-year-old female developed serotonin syndrome after receiving darunavir/ritonavir, esomeprazole, and citalopram (an enantiomer of citalopram). Escitalopram elimination was inhibited through CYP2C19 and CYP3A4 and genotyping revealed poor CYP2C19 and CYP2D6 metabolism [7]. All individuals had symptom improvement 24 to 72 h after drug discontinuation. These cases suggest greater risk of toxicity with impaired citalopram metabolism [6,7].

4. Conclusion

Although rare, single citalopram overdose may be associated with severe serotonin syndrome. Patients with impaired metabolism due to altered enzyme function may be at increased risk of toxicity. Further investigation is warranted to understand the impact of enzyme genotype on toxicity.

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Prior presentations

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Declaration of Competing Interest

The authors report no conflict of interest.

References