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TOXICOLOGY OBSERVATION

Citalopram Overdose: a Fatal Case

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Abstract
Background Citalopram is a selective serotonin reuptake inhibitor (SSRI) with cardiac and neurologic toxicities as well as the potential for serotonin syndrome. In most instances, patients recover fully from toxic ingestions of SSRIs. We describe a fatal case of a citalopram overdose.
Case Report A 35-year-old woman presented to the emergency department after having witnessed seizures at home. An empty citalopram prescription bottle was located, and an intentional overdose was suspected. At the scene, she was found to be in cardiac arrest with pulseless electrical activity and underwent cardiopulmonary resuscitation, including intravenous epinephrine and bicarbonate. In the emergency department, her physical exam was notable for cough and gag reflexes and movement in all extremities with increased muscle tone and tachycardia. Her initial postresuscitation ECG showed sinus rhythm with QRS 92 ms and QTc 502 ms. Her temperature was initially normal, but she rapidly became febrile to 41.8 °C shortly after admission. She was treated symptomatically and with cyproheptadine for suspected serotonin syndrome (SS) but became increasingly hemodynamically unstable over the next 6 h and then developed torsades des pointes (TdP) progressing to pulseless, wide complex tachycardia. She underwent cardiopulmonary resuscitation (CPR) for approximately 50 min but ultimately expired. Postmortem serum analysis revealed a citalopram concentration of 7300 ng/mL (therapeutic range 9–200 ng/mL) and THC, but no other non-resuscitation drugs or substances.
Case Discussion Citalopram overdoses often have only mild to moderate symptoms, particularly with ingestions under 600 mg in adults. However, with higher doses, severe manifestations have been described, including QTc prolongation, TdP, and seizures. Serotonin syndrome has also been described in SSRI overdose, and our patient exhibited signs consistent with SS, including increased muscle tone and autonomic dysregulation. Our patient's serum concentration suggests a massive overdose, with major clinical effects, possible SS, and death.
Conclusions Although most patients recover from citalopram overdose, high-dose ingestions can produce severe effects and fatalities may occur. In this case, it is likely that the patient's delayed presentation also contributed significantly to her death. The clinician must be aware of the potential for large ingestions of citalopram to produce life-threatening effects and monitor closely for the neurologic, cardiovascular, and other manifestations that, in rare cases, can be fatal.

Keywords Citalopram · Overdose · Torsades des pointes · Serotonin syndrome · Death

Introduction

Citalopram is a selective serotonin reuptake inhibitor approved by the FDA in 1988 for the treatment of major depression and is widely prescribed worldwide. It is highly selective for 5-HT reuptake receptors with minimal effect on norepinephrine and dopamine receptors [1]. In general, selective serotonin reuptake inhibitors (SSRIs) have been shown to be safer in overdose than tricyclic antidepressants (TCAs) and the rate of suicide from antidepressant intoxication decreased after their introduction [2]. However, citalopram is considered

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to have the most potential for cardiac and neurologic toxicity among the SSRIs and there are numerous case reports of these toxicities in overdose [3–5]. Serotonin syndrome may also occur following overdose [6, 7]. Yet even with high-dose ingestions, most patients fully recover. There have been very few reports of fatal citalopram overdoses without co-ingestants [5, 8]. We report a case of an isolated, citalopram overdose resulting in death.

Case Report

A 35-year-old, 82.5-kg female who had a past medical history of depression was brought into our emergency department after having a series of witnessed seizures at home. Her boyfriend reported she had several convulsive episodes approximately 24 h prior to admission which resolved spontaneously and which may have been when she took her overdose. She was last seen 10 min before being witnessed to have another seizure, after which she became cyanotic and pulseless and 911 was called. She was found to be in pulseless electric activity (PEA) by paramedics. The pre-hospital resuscitation included bystander cardiopulmonary resuscitation (CPR), epinephrine 1 mg×5, paramedic CPR, bag-valve-mask ventilation, IV NS 500 mL bolus plus infusion, naloxone 0.4 mg, OG tube, and LMA airway, with airway monitoring by capnography.

Her out-of-hospital CPR was successful in obtaining return of spontaneous circulation. The boyfriend reported he had found her empty citalopram bottle prior to the beginning of the seizure episodes, although she had denied overdose. She had no prior history of seizures. Her only medication was citalopram. She had a remote history of methamphetamine use and was also reported to be using alcohol and marijuana.

On arrival to the emergency department, she again developed PEA which responded to treatment with two ampules of IV sodium bicarbonate and 1 mg of IV epinephrine. She was intubated for airway protection. Postresuscitation, her temperature was 35.6 °C, blood pressure 79/42 mmHg, pulse 124, and respiratory rate 22/min. Neurologic exam was significant for increased tone in all extremities, 1–2+ deep tendon reflexes, absent deep tendon reflexes, nonreactive pupils, and the presence of cough and gag reflexes. Spontaneous clonus was not present, but induced clonus was either not evaluated or not documented. She was moving all extremities spontaneously. Cardiovascular exam revealed tachycardia. Lungs were clear bilaterally, and abdominal exam was unremarkable. No magnesium was documented as having been given in the pre-hospital phase or in the emergency department.

Her initial ECG showed sinus tachycardia at 117 beats per min (bpm), QT 360 ms, QTc 502 ms (with Bazett's formula), and QRS 92 ms (Fig. 1). Selected initial laboratory studies are shown in Table 1. Urine toxicology screen (EMIT II Plus, Siemens Healthcare Diagnostics, Inc.) was positive for cannabinoids and negative for amphetamines, barbiturates, benzodiazepines, cocaine, methadone, and opiates. Over the course of her hospitalization, her creatinine increased from 0.9 to 1.29 mg/dL, and her AST/ALT increased from 300/153 to 469/207 mg/dL just prior to death. A CT scan of the head revealed no acute abnormalities.

She was admitted to the medical intensive care unit, and subsequent ECG showed a heart rate of 120 bpm and a widening QRS of 122 ms on repeat measurement, and she was treated with one ampule (50 mEq) of sodium bicarbonate by IV bolus, without response. She was given magnesium 2 g IV×3 for her QTc prolongation. She was also given midazolam 5 mg IV×1 for treatment of her seizures. Core temperatures via urinary bladder thermistor catheters were normal on arrival. At 2 h post-arrival, temperatures increased to >38 °C (100.4 °F) and continued to increase despite active cooling measures. Her peak core temperature was 41.8 (107.2 °F) at her terminal event approximately 5 h after arrival. She was also treated with 12 mg of oral cyproheptadine for suspected serotonin syndrome. Approximately 6 h after arrival, she was noted to still have a widened QRS at 120 ms and to have a further increase in the QTc to 512 ms (with Bazett's formula; rate 119 bmp and QT 364 ms). The patient then developed a wide complex tachycardia suspected to have torsades des pointes (Fig. 2). Her ECG showed a heart rate of 201 bpm, QRS 160 ms, QT 194 ms, and QTc 355 ms (with Bazett's formula). She lost pulses and underwent CPR for 50 min but ultimately expired.

Autopsy findings included a blood citalopram concentration of 7300 ng/mL (therapeutic range 9–200 ng/mL), and only THC was found on broad postmortem forensic toxicology testing.

Discussion

This patient took a massive overdose of citalopram and had repetitive seizures and an out-of-hospital cardiopulmonary arrest, ultimately resulting in a fatality. Despite the relatively favorable safety profile of SSRIs, severe overdoses can be lethal. The patient demonstrated severe manifestations of citalopram toxicity including cardiac and neurologic effects and features consistent with serotonin syndrome.

In a small case series of isolated citalopram overdoses reported to a poison center, symptoms were more severe with ingestions greater than 600 mg, leading to seizures in 18 %, and in patients ingesting greater than 1900 mg, seizures were present in 47 % [9]. In citalopram overdoses under 600 mg, neurologic symptoms were generally mild and limited to dizziness, tremor, drowsiness, palpitations, tachycardia, and somnolence [9, 10]. It should be kept in mind that poison center data is subject to reporting bias, often secondhand, and without confirmatory drug levels and that these dose-response relationships have not been validated in a prospective study.

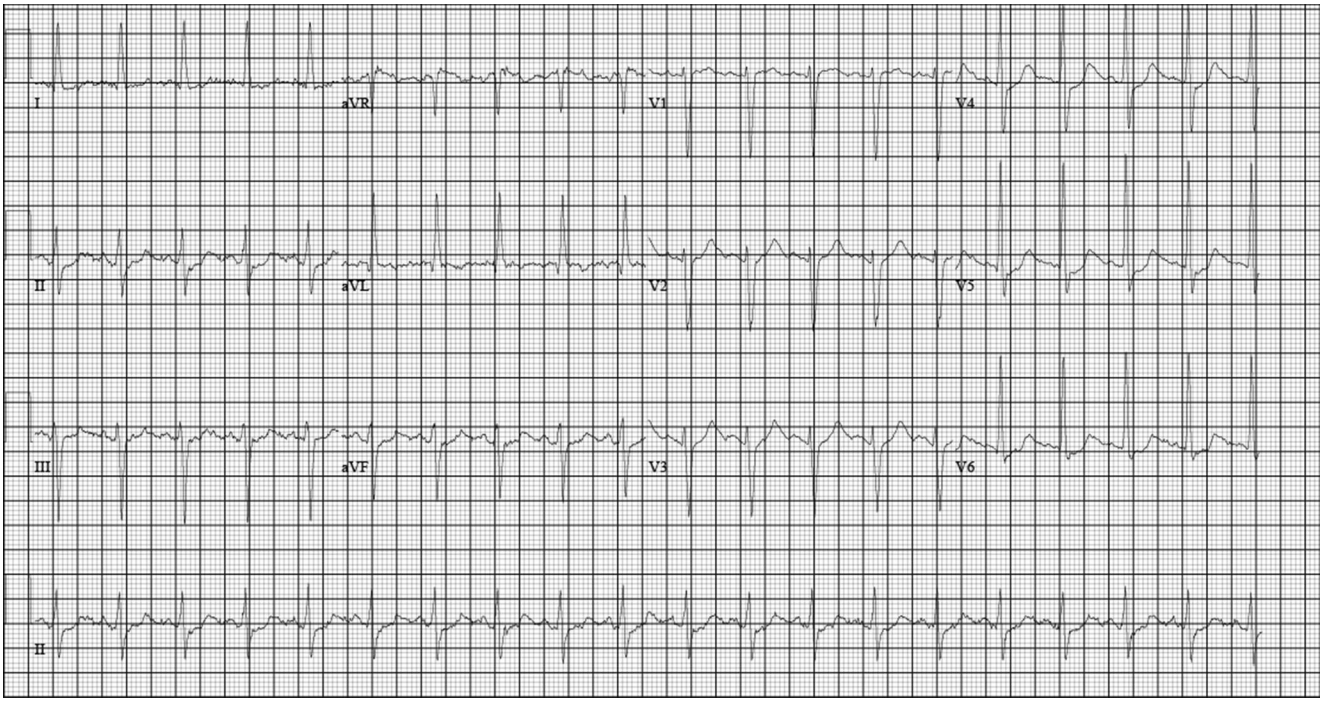

Fig. 1 Initial ECG with ventricular rate 117 bpm, PR interval 154 ms, QRS duration 92 ms, and QT/QTc 360/502 ms

At higher doses, citalopram overdose is also known to have a greater potential than other SSRIs for cardiotoxicity in the form of QTc prolongation, arrhythmias, and conduction disturbances [11]. The mechanism of cardiac toxicity is thought to be, in part, mediated by one of its metabolites, didemethylcitalopram (DDCT), and its blockade of the inward rectifier potassium channel [12]. As a consequence of QT prolongation, torsades des pointes has also been described in citalopram overdose [5] and was seen in our patient.

Table 1 Initial laboratory studies

Sodium	148 mmol/L
Potassium	3.4 mmol/L
Chloride	103 mmol/L
Bicarbonate	17 mmol/L
BUN	8 mg/dL
Creatinine	0.92 mg/dL
Calcium	7.3 mg/dL (corrected 8.2)
Magnesium	3.0 mg/dL
Glucose	311 mg/dL
WBC	$27.9\times10^3/\mu L$
Hgb	12 g/dL
Platelets	$223\times10^3/\mu L$
CK	1099 units/L
BNP	4579 pg/mL
Trop	0.182 ng/mL
Lactate	19.9 mg/dL
AST/ALT	300/153 mg/dL
Albumin	2.9 mg/dL

It is unclear why she had an elevated magnesium level on presentation. It is possible that she received magnesium in the pre-hospital or emergency department settings without documentation. Her subsequent magnesium, after three 2 g boluses, was within the normal range. Our patient's signs of renal and hepatic injury are likely related to hypoperfusion during episodes of PEA and may have had some contribution by her hyperthermia. Seizures usually occur early in the course of a citalopram overdose [13], and their presence 24 h prior to presentation suggests an overdose at that time. The presence of ongoing seizures and temperature dysregulation may also have been related to persistent high drug levels and/or cerebral injury from hypoperfusion. Torsades des pointes (TdP) is related to prolongation of the QT interval but can occur at any time while the QT is prolonged [14]. Thus the development of TdP more than 24 h into the overdose is not surprising. Assessment of QT prolongation and TdP risk, however, is complex and controversial, with Bazett's formula, which was applied here, tending to overestimate TdP risk at higher heart rates and to underestimate the risk at low heart rates [15]. A QT interval nomogram to correct for this tendency has been developed [15]. Although the TdP risk by this nomogram appears to be less than that by Bazett's formula, it was still increased during the time preceding her arrhythmic event. The dose taken by our patient is unknown, but her blood concentration suggests a very large, acute overdose. There has been only one previous report of a higher serum concentration. In that case, a 22-year-old female was found dead at home after a suspected intentional overdose of citalopram. Based on empty pill packages found at the scene, the amount ingested was presumed to be 2880 mg (40 times the

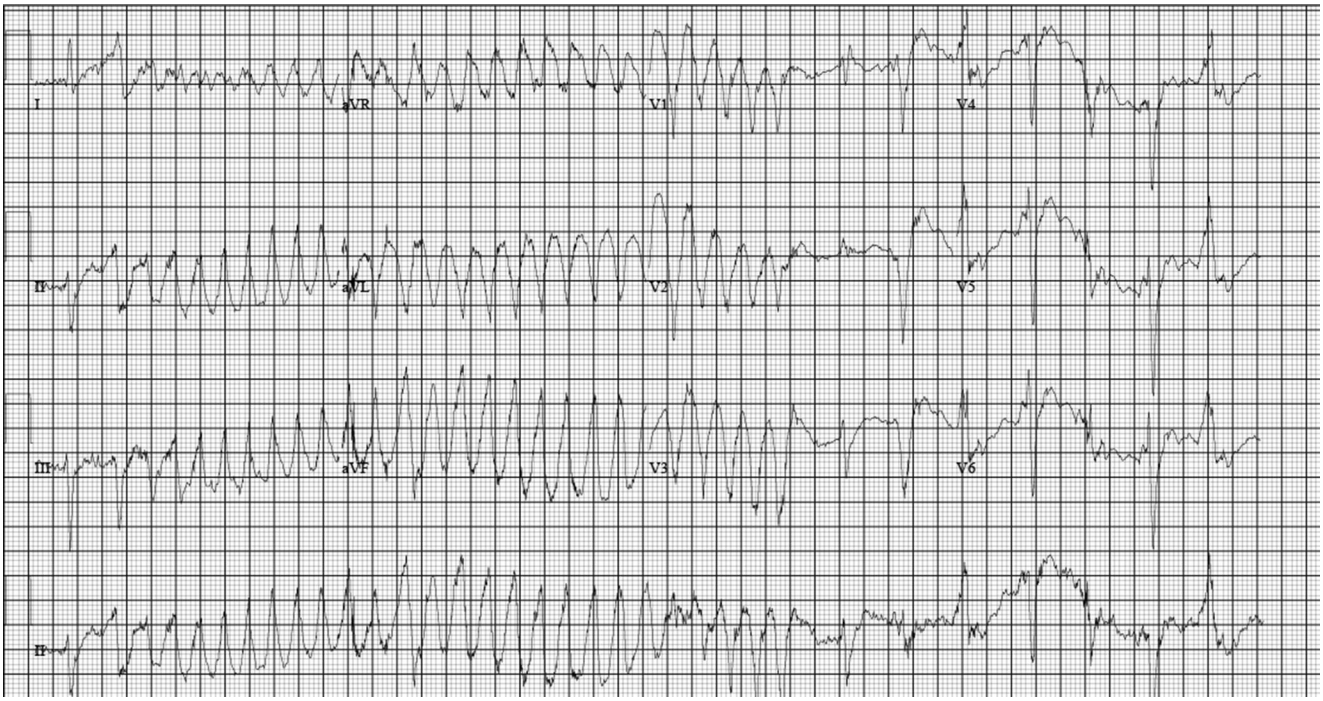

Fig. 2 Subsequent ECG pre-arrest, with ventricular rate 201 bpm of indeterminate rhythm, QRS duration 160 ms, and QT/QTc 194/355 ms

daily dose) and the serum concentration of citalopram was reported to be 11,600 ng/mL [4].

Some of the patient's findings may have resulted from ischemic injury, including temperature dysregulation. On the other hand, our patient's signs are also consistent with serotonin syndrome, including fever >38 °C and rigidity on exam. Given her presentation in extremis, she did not have spontaneous clonus and, while her status would have allowed examination for induced clonus [16], its presence or absence was not documented. The incidence of serotonin syndrome following an acute overdose of SSRI agents is unknown, but in one series, serotonin syndrome occurred in 14 % of SSRI overdoses [17]. The diagnosis of serotonin syndrome in this case is difficult to make with greater certainty because of the many unknowns resulting from the delayed presentation. Regardless, the delay in presentation, out-of-hospital seizures and cardiac arrest also undoubtedly contributed to the patient's death.

Management of a citalopram overdose generally includes symptomatic and supportive care including airway protection and ventilator support, treatment of seizures, observation for cardiac conduction abnormalities, optimization of electrolytes associated with QT interval (K, Ca, Mg), and temperature control. Patients with suspected serotonin syndrome are generally managed with withdrawal of the offending agent(s) and symptomatic and supportive care but can also be treated with the serotonin receptor antagonist cyproheptadine [18]. Evidence for its effectiveness, however, is limited to some animal data and case reports [19–21]. Cyproheptadine may be of limited usefulness in severe serotonin syndrome as most positive reports of its effectiveness have been in more mild cases. Also, effectiveness may be limited by the oral route of administration and unpredictable absorption in critically ill patients [18]. QT prolongation, however, is not reported at therapeutic doses [22], and it was felt that the potential benefits of this drug outweighed the risks. The suggested parenteral agent for severe serotonin syndrome, chlorpromazine, also has concerns, including the potential for hypotension and exacerbation of QT prolongation at therapeutic doses [23].

Conclusion

Although most patients recover from citalopram overdose, high-dose ingestions can produce severe effects and fatalities may occur. In this case, it is likely that the patient's delayed presentation also contributed significantly to her death. The clinician must be aware of the potential for large ingestions of citalopram to produce life-threatening effects and monitor closely for the neurologic, cardiovascular, and other manifestations that, in rare cases, can be fatal.

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Conflict of Interest The authors declare no conflicts of interest.

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