Citalopram Overdose: Late Presentation of Torsades De Pointes (TdP) With Cardiac Arrest

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ABSTRACT

Introduction: Citalopram overdose may produce bradycardia, QT prolongation, and torsades de pointes (TdP). A cardiotoxic metabolite may be responsible for the delayed onset of cardiotoxicity. Although some authorities recommend a minimum of 24 hours of observation following citalopram overdose, a recent analysis suggested that dysrhythmias rarely occur beyond 13 hours post-ingestion. We present a case of citalopram overdose with a substantially delayed onset of cardiac toxicity.

Case Report: A 36-year-old woman complained of shakiness, numbness in the arms, and palpitations that began approximately 32 hours after ingesting 50 (20-mg) tablets of citalopram. Her initial vital signs were: blood pressure, 84/44 mmHg; pulse, 102–150/minute; respirations, 17/min; temperature, 99.3° F (37.3° C). Her initial ECG showed sinus rhythm with a prolonged corrected QT interval (572 msec) with paroxysmal, self-limited runs of wide-complex tachycardia that appeared multifocal in nature.

Approximately 20 minutes after presentation, she experienced self-terminating TdP, with transient hypotension and loss of consciousness. Her serum citalopram concentration (33 hours post-ingestion) was 477 ng/mL (therapeutic: 40–110 ng/mL); desmethylcitalopram concentration was 123.2 ng/mL (therapeutic: 14–40 ng/mL). She was treated with magnesium and lidocaine, and her corrected QT interval remained abnormal for 24 hours after presentation.

Discussion: Citalopram overdose can produce life-threatening cardiac toxicity with a clinical onset that may be delayed beyond a routine observation period of 6 hours. Once the QT interval is prolonged, it seems prudent to prolong the observation period.

INTRODUCTION

Citalopram and escitalopram are widely prescribed for the treatment of depression in over 70 countries and to over 30 million patients [1]. Daily citalopram doses can range from 20 to 60 mg. Like the other selective serotonin reuptake inhibitors (SSRIs), citalopram and escitalopram are potent inhibitors of neuronal serotonin uptake, without effects on the reuptake of either norepinephrine (NE) or dopamine (DA) [2]. As a class, the SSRIs are considered to have a safe cardiovascular profile, particularly when compared to the cyclic antidepressants [3,4]. Unlike tricyclic antidepressants, citalopram has only a weak inhibitory effect on rectifying K^+ channels (I_{kr}) [5]. Animals exposed to supratherapeutic concentrations of citalopram failed to exhibit cardiotoxic effects [2]. Similarly, in therapeutic doses in humans, citalopram does not exert a significant effect on PR, QRS, or QT intervals [2].

In contrast to the premarketing data, however, the postmarketing literature contains multiple case reports demonstrating that citalopram may produce significant cardiac toxicity in overdose [6–10]. It is postulated that a metabolite, didesmethylcitalopram, inhibits cardiac K^+ and Ca^{2+} channels [11–13]. In overdose, this produces bradycardia, QT prolongation, and TdP [4,6–10,14], which usually develops within the first 24 hours post-exposure. Based on reported cases in which cardiac toxicity

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developed beyond the conventional 6-hour observation period for asymptomatic poisoned patients [10,15], some authorities routinely recommend a minimal observation period of 24 hours following citalopram overdose [16]. In contrast, a recent case series with toxicokinetic modeling suggested that dysrhythmias beyond 13 hours post-ingestion are exceedingly rare [17]. It is essential to define the time delay to the initial onset toxicity, as this will greatly impact observation and admission guidelines.

We present a case of a patient with citalopram overdose who had a substantially delayed onset of cardiac toxicity.

Case Report

A 36-year-old woman presented to the hospital complaining of shakiness, numbness in the arms, and palpitations. The following history was corroborated by the patient's sister. Approximately 10:00 PM on a Saturday, in a suicide attempt, the patient ingested 50 tablets of citalopram (20 mg) with some wine. On Sunday, she was lethargic and remained at home all day. On Monday, when she awoke, the patient noted the above complaints and was brought to the hospital.

Her past medical history was remarkable for bulimia and anorexia nervosa since age 15, alcohol abuse since age 21, and previous suicide attempts. Her only current medication was citalopram, which was started at a dose of 20 mg/day, 3 weeks prior to admission. No other prescription medications were available.

On physical examination she was awake and alert, but appeared somewhat anxious with the following vital signs: blood pressure, 84/44 mmHg; pulse, 102–150/minute; respirations, 17/min; temperature, 99.3° F (37.3° C). Pertinent findings on physical examination included normal pupillary function, a chest that was clear to auscultation, irregular heart sounds without murmurs, rubs, thrills or gallops, normal bowel sounds, and moist mucous membranes.

Her initial ECG on arrival in the emergency department (ED) showed sinus tachycardia with runs of multifocal wide-complex tachycardia. The corrected QT interval (Bassett's formula) ranged between 572 to 600 msec (*Figure 1*). Initial laboratory studies are shown in *Table 1*.

While in the ED, multiple short runs of nonsustained wide-complex tachycardia were observed on the monitor. During these episodes she remained conscious, but reported palpitations and weakness. The patient received 2 g $MgSO_4$ intravenously, and her rhythm changed to bigeminy. Lidocaine (100 mg) was given intravenously with no effect. Approximately 20 minutes after presentation, the patient experienced self-terminating TdP, with transient hypotension and loss of consciousness (*Figure 2*). Following recovery, isoproterenol was infused intravenously at 10 mcg/mL, and she remained in sinus rhythm. Supplemental intravenous potassium was also given,

Table 1: Laboratory Studies at Presentation

Sodium	133 mmol/L
Potassium	3.1 mmol/L
Chloride	77 mmol/L
Bicarbonate	34 mmol/L
Blood urea nitrogen	12 mg/dL (4.3 mmol/L)
Creatinine	1.2 mg/dL (106 μmol/L)
Glucose	105 mg/dL (5.8 mmol/L)
Calcium	9.2 mg/dL (2.3 mmol/L)
Inorganic phosphorus	0.9 mg/dL (0.29 mmol/L)
Magnesium	2.5 mg/dL (1.25 mmol/L)

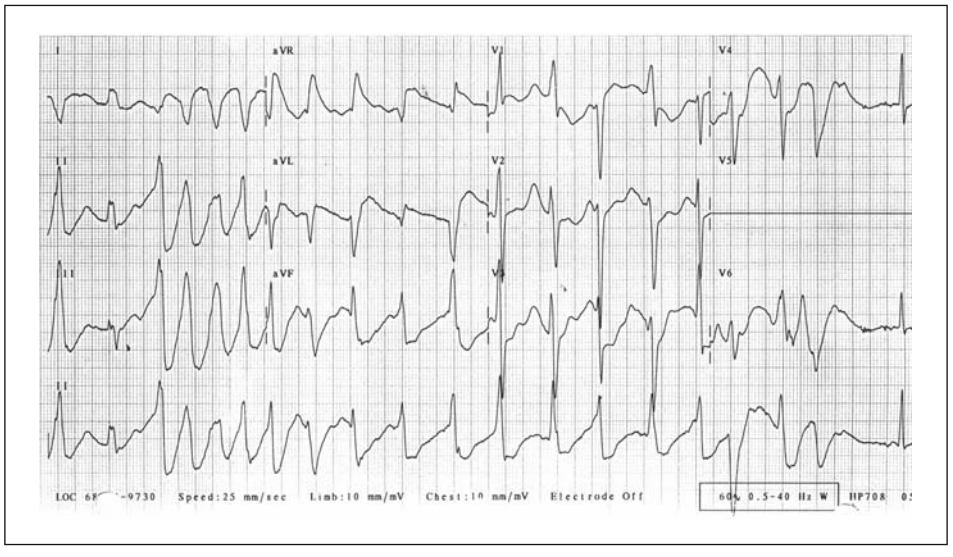

Figure 1: Initial ECG showing sinus tachycardia with runs of multifocal wide-complex tachycardia. The QTc ranges between 572 and 600 msec.

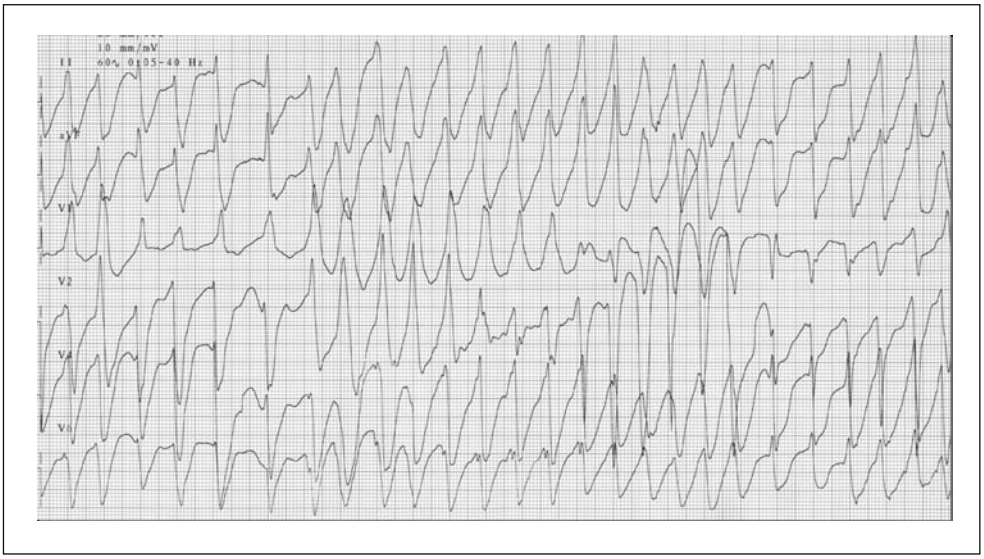

Figure 2: Self-terminating TdP with syncope.

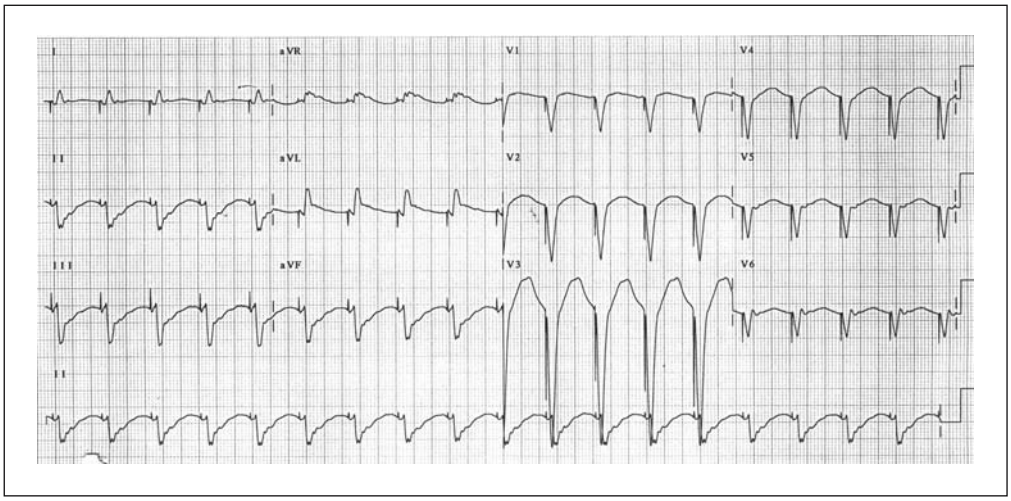

Figure 3: Paced at a rate of 110 bpm, no dysrhythmias noted.

and a temporary transvenous pacemaker was inserted for overdrive pacing.

The patient was transferred to the CCU where she remained paced at a heart rate of 110 bpm for 24 hours, during which time no further dysrhythmias were noted (*Figure 3*). An echocardiogram was interpreted as normal and her troponin peaked at 2.4 ng/mL. A repeat ECG taken 24 hours after presentation showed a corrected QT interval of 529 msec. Twenty-four hours later, her corrected QT interval had nearly normalized to 442 msec (*Figure 4*). She was subsequently discharged in excellent condition.

Toxicology testing of her serum at presentation was negative for aspirin and acetaminophen, and her urine was negative for drugs of abuse. Her serum citalopram concentration (obtained approximately 33 hours post-ingestion) was 477 ng/mL (therapeutic: 40–110 ng/mL) and her desmethylcitalopram concentration was 123.2 ng/mL (therapeutic: 14–40 ng/mL).

DISCUSSION

This case describes the delayed presentation of citalopram-associated TdP documented with ECG findings and elevated citalopram and desmethylcitalopram concentrations obtained 33 hours after the reported time of exposure. It is unclear what effect the patient's eating disorder or alcohol abuse had on her clinical course, but the normal serum magnesium and calcium concentrations and the marginally low potassium concentration suggest that cardiac toxicity was largely unrelated to these conditions.

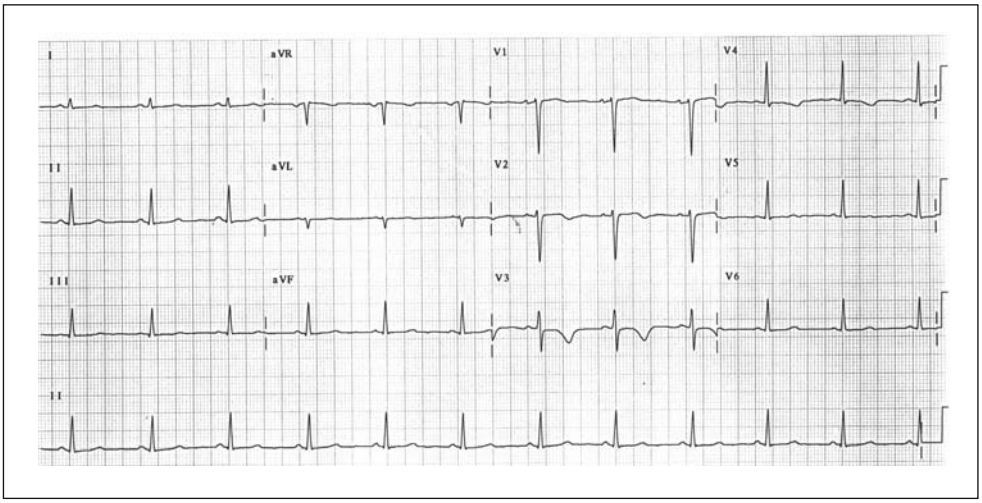

Figure 4: Repeat ECG at 48 hours after presentation; QTc 442 msec.

Previous studies have shown an increased risk of dysrhythmias in women using QT interval–prolonging drugs. It is worth noting that our patient's QTc interval corrected entirely during the observation period in the hospital.

In therapeutic doses, the favorable safety profile of citalopram may result from its ability to inhibit L-type calcium (Ca^{2+}) channels, an effect that may prevent TdP [2]. Thus, like amiodarone, although QT prolongation may occur via inhibition of a cardiac-delayed rectifier potassium channel (Ikr), TdP does not commonly occur. Since a metabolite of citalopram is responsible for cardiac toxicity, the delayed onset reported in this and other cases may implicate pharmacogenetic variability as a cause. Citalopram is metabolized by CYPs 2C19, 3A4, and 2D6. These enzymes either demonstrate significant genetic variability (2C19 and 2D6) or are highly susceptible to inhibitors (3A4), thus creating the possibility of individuals with either unique sensitivity (extensive metabolizers who form disproportionate amounts of cardiotoxic metabolite) or those with delayed toxicity (slow metabolizers).

Unfortunately, like most intentional overdose patients, the most important part of this patient's history (i.e., the time of ingestion) is also the most unreliable. It is conceivable that the patient experienced short runs of ventricular dysrhythmias prior to her presentation to the ED. However, her first clinically significant effect (i.e., loss of consciousness) occurred 33 hours post-ingestion. It remains unclear how long to observe patients who do not develop QT interval prolongation following citalopram ingestion. However, this report adds to the existing cases that suggest that dysrhythmias may be delayed [10,15].

CONCLUSION

Citalopram overdose can produce life-threatening cardiac toxicity whose first manifestation may be delayed beyond a routine observation period. This suggests that until more is understood about the clinical effects of citalopram overdose, prolonged observation may be prudent for those overdose patients with citalopram-induced QT interval prolongation.

The authors have no potential financial conflicts of interest to report.

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