

QT Prolongation and Torsades de Pointes Following Overdose of Ziprasidone and Amantadine

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INTRODUCTION

The Food and Drug Administration (FDA) approved Ziprasidone, a second-generation atypical antipsychotic, in February 2001 [1]. Ziprasidone has a unique receptor profile that includes high-affinity antagonist activity at dopamine D₂ receptors, inverse agonist activity at serotonin (5-HT)_{2A} receptors, agonist activity at 5-HT_{1A} receptors, and a relatively high affinity for serotonin and norepinephrine transporters [2]. It is recommended for the treatment of conditions that include, but are not limited to, acute mania, bipolar disorder, schizophrenia, and acute psychotic agitation [3–7].

Antipsychotic drug-induced QTc prolongation is of major concern because epidemiologic data and case-control studies have indicated an increased rate of sudden death in psychiatric patients taking antipsychotic drugs [8–11]. In 2002, just one year after FDA approval, a report issued from the FDA noted that safety studies comparing ziprasidone and other QT-prolonging drugs were lacking, and “an additive effect of ziprasidone and other drugs that prolong the QT interval cannot be excluded” [12]. Studies found that patients with dementia-related psychosis, treated with atypical antipsychotic medications, including ziprasidone, were at increased risk of death when compared to placebo treated patients. Following the findings of these studies, the FDA in 2005 recommended a black box warning [13]. Subsequently, a recommendation was placed in the product labeling that the agent should not be administered to patients who have significant cardiovascular illness or electrolyte imbalance or are receiving other agents that may prolong the QT interval [14].

Ziprasidone is widely reported to cause QTc prolongation, but without increased risk of Torsades de Pointes (TdP) [2,15–19]. However, very recent literature reports may suggest the possibil-

ity of TdP [20,21]. This case report describes a 30-year-old woman who overdosed with ziprasidone, amantadine, and ibuprofen, and who displayed QT prolongation leading to TdP.

CASE REPORT

A 30-year-old woman was found unresponsive by a family member. The family reported that she was depressed ever since her father died 2 weeks previously, and 5 hours earlier that day she voiced a suicidal threat to her family. Emergency Medical Technicians found empty bottles of ziprasidone (60 mg tablets), amantadine (100 mg tablets), and ibuprofen (600 mg tablets) present on the floor near the patient. The family reported that she fell from her wheelchair to the ground and sustained minor trauma to the right leg.

Her past medical history was remarkable for mental retardation and depression with psychotic features. Her regular medications included ziprasidone (60 mg twice daily) and amantadine (100 mg twice daily).

On arrival to the Emergency Department, the patient's vital signs were: blood pressure, 118/76 mmHg; pulse rate, 60 beats/min; respiratory rate, 16 breaths/min; and oral temperature, 98.6 °F. She was lethargic but rousable to voice. Her pupils were equal, round, and reactive to light. The head, eyes, ears, nose, and throat examinations were unremarkable. She was in no respiratory distress and her breath sounds were bilaterally clear. Auscultation of heart tones revealed regular rate and rhythm without murmurs, rubs, or gallops. Abdominal examination revealed normal bowel sounds without tenderness or organomegaly. Skin examination was normal. Examination of the extremity revealed moderate ecchymosis of the right lower extremity overlying the popliteal fossa, but no deformity and 2+ pulses distally. Neurological examination was not

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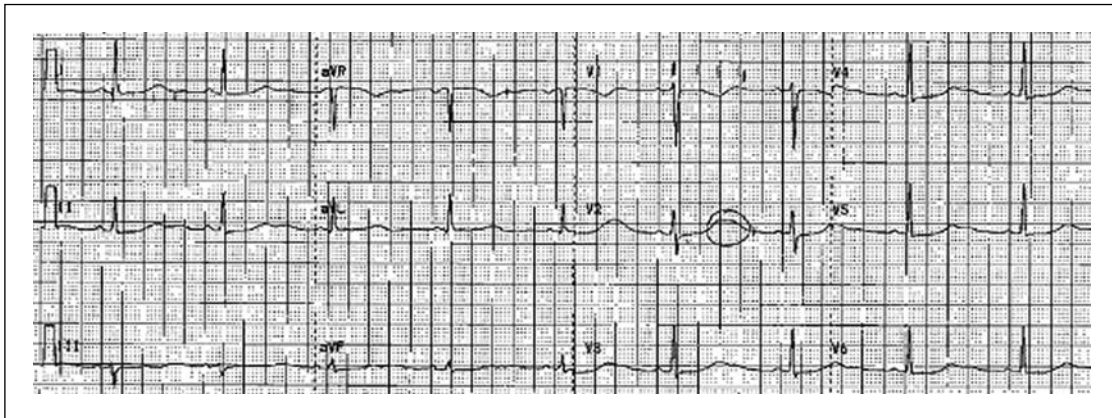


Figure 1: Initial electrocardiogram taken in the Emergency Department. In lead II, the QT is 800 ms, which combined with a pulse of 55/minute corresponds to a calculated QTc (Bazett) of 770 ms.

completely assessed due to poor cooperation with the examination, but she was moving all extremities without a focal neurological deficit.

The patient was attached to a cardiac monitor and intravenous access was obtained. An electrocardiogram (*Figure 1*) performed on arrival to the Emergency Department and approximately 3 hours after her exposure, was notable for sinus bradycardia at 55 beats/min with a normal axis, QRS of 92 milliseconds (ms), and a markedly prolonged QT of 800 ms in lead II with a QTc (Bazett's correction) of 770 ms [22]. There was no terminal 40-ms right axis deviation of the QRS complex. We noted occasional premature ventricular contractions on the bedside cardiac monitor.

Laboratory evaluation was notable for a potassium of 3.0 mEq/L and a magnesium of 1.9 mEq/L. Results of bicarbonate, creatinine, complete blood count, calcium, cardiac biomarkers, and urinalysis were within normal limits. Serum acetaminophen, ethanol, salicylates, and a pregnancy test were all negative.

In the emergency department, she received one liter of normal saline intravenously, oral potassium replacement therapy, and was placed on 1:1 observation. The plan was to clear her medically and admit her to the psychiatric service. Approximately 8 hours after arrival to the ED and while waiting for an inpatient bed, the patient lost consciousness and showed a simultaneous appearance of a wide complex tachydysrhythmia on the monitor (*Figure 2*). The patient immediately received a succession of 5 defibrillations (monophasic defibrillator—100 J, 150 J, 200 J, 200 J, 200 J) with subsequent return of spontaneous circulation and a normal sinus rhythm. The patient was endotracheally intubated without pre-medications during the course of the resuscitation. No chemical antidysrhythmics or magnesium replacement was administered prior to defibrillation and return of spontaneous circulation.

Post-resuscitation, she had a follow-up electrocardiogram that revealed a normal sinus rhythm with an excessively prolonged QT in lead II (720 ms) and a QTc (Bazett) that decreased to 750 ms (*Figure 3*). She received an intravenous magnesium bolus of 2 grams, followed by an infusion of 2.8 gm/hour. She received an additional 40 mEq intravenous potassium chloride over 1 hour



Figure 2: Electrocardiogram during cardiac arrest, taken approximately 8 hours after the patient's arrival to the Emergency Department. The torsades de pointes morphology is readily apparent.

and a total of 90 mEq over the first 24 hours. Amiodarone 150 mg was intravenously loaded over 30 minutes. The patient was admitted to the Cardiac Care Unit (CCU) and the Poison Control Center was consulted.

After arrival in the CCU, amiodarone was discontinued. Her QTc remained approximately 540 ms, and the subsequent 12 hours were complicated by episodes of sustained ventricular tachycardia (*Figure 4*). On CCU day 1, an isoproterenol infusion was initiated (2 mcg/min) in an attempt to achieve chemical overdrive pacing. No further episodes of TdP or ventricular tachycardia occurred once the QTc shortened below 500 ms.

Her CCU course was complicated by bilateral pulmonary infiltrates on CCU day 3 and urosepsis initially detected from a urine specimen drawn on day 4. Urine and blood cultures drawn on day 4 grew *E. coli* and her hemodynamics worsened, with three vasopressors required to maintain perfusion. Subsequently, she developed disseminated intravascular coagulation; and due to concerns

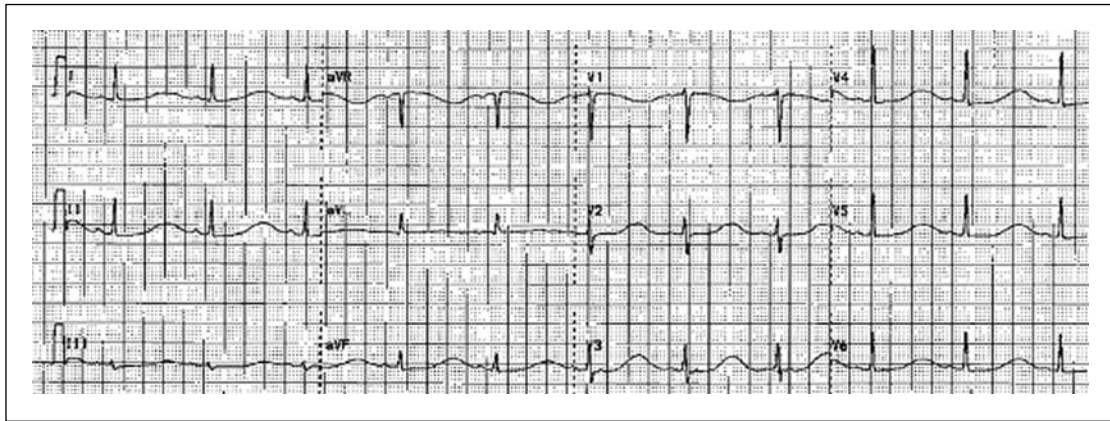


Figure 3: Electrocardiogram taken in the Cardiac Intensive Care Unit just 3 hours after torsades de pointes cardiac arrest. In lead II, the QT interval is 720 ms, which combined with a pulse of 65/minute corresponds to a QTc (Bazett) of 750 ms.

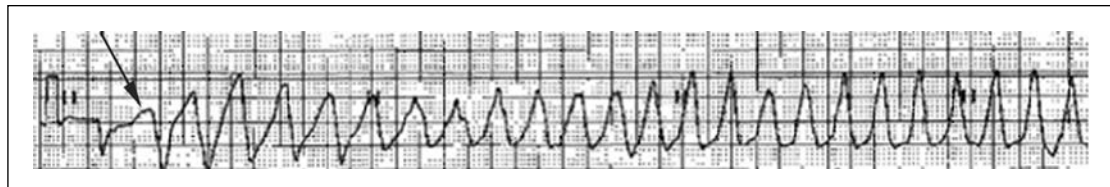


Figure 4: Rhythm strip taken in the Cardiac Intensive Care Unit following the initial resuscitation demonstrates one initial narrow QRS complex followed by a fusion beat (arrow) and subsequent sustained ventricular tachycardia.

of pulmonary embolism, computed tomography was performed with evidence of right lower extremity deep venous thrombosis as well as pulmonary embolus. She expired on CCU day 10. A post-mortem revealed evidence of sepsis and a pulmonary embolism.

DISCUSSION

Given the history and clinical circumstances, we believe the episode of TdP was secondary to drug-induced QT prolongation. This history and findings at the scene were clearly consistent with overdose of her medications, which included ziprasidone and amantadine. Although we did not ascertain confirmatory serum levels, the patient openly admitted to suicidal overdose of her medications, and empty ziprasidone and amantadine bottles were found nearby at the scene. Following her initial cardiac arrest, she suffered numerous nosocomial complications including urosepsis, disseminated intravascular coagulation, and subsequent pulmonary embolism which together resulted in death.

Ziprasidone prolongs the QTc by blockade of potassium channels and subsequent interference with the rectifying potassium current (I_{Kr}) [23–24]. In a study of 31 patients, ziprasidone, at a dose of 160 mg/day, increased the mean QTc by 16 ms [25]. In placebo-controlled trials, ziprasidone, at 160 mg/day, increased the mean QTc by 10 ms [26].

A meta-analysis from Justo and colleagues suggests that the most prevalent risk factors for development of psychotropic drug-induced TdP include the female gender, presence of heart disease, hypokalemia, long QT syndrome, high dosing, and concomitant use of another QT-prolonging drug [27,28]. Of these risk factors, this patient had at least three, including amantadine co-ingestion and presence of hypokalemia [29–31]. However, the patient received oral potassium therapy hours before the occurrence of TdP; the only case report of amantadine-induced TdP was in a patient with a presentation of cardiac arrest early in the course of the overdose, with ventricular fibrillation being exacerbated, not improved, by administration of isoproterenol.

This patient had early signs (prolonged QT) but an 8-hour delay to occurrence of symptoms (TdP) during her Emergency Department course. When this period is added to the time from ingestion, this represents an important delay for initial symptoms of cardiac toxicity. In addition, recurrent episodes of sustained ventricular tachycardia over the first 12 hours in the CCU were unexpected since ziprasidone has a half-life of 4–10 hours and does not form any active metabolites [24]. In this case, an undescribed pharmacokinetic interaction between ziprasidone and amantadine cannot be ruled out as the cause of delayed dysrhythmias.

In conclusion, ziprasidone is currently regarded in the literature as a drug that does not induce TdP despite both an FDA-recommended black box warning and well-established

prolongation of the QTc [2,15–19,13,2,4,25,26]. We reported the case of marked QT prolongation and TdP following overdose of ziprasidone and amantadine.

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

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