



Flecainide overdose presenting with long QT and acute Takotsubo cardiomyopathy[☆]

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Introduction

Takotsubo cardiomyopathy is a rare type of reversible cardiomyopathy characterized by the development of left-ventricular (LV) apical ballooning in the absence of significant coronary arterial disease. Initially described in Japan during the 1990s [1], this diagnosis has become more common with advanced cardiac imaging modalities and increasing awareness. The etiology and pathogenesis of Takotsubo remain unclear, but it often follows extreme emotional or physical stress [1]. Catecholamine-induced myocardial stunning and autonomic dysfunction have becoming leading hypotheses [2].

Echocardiography and cardiac catheterization are essential tools in the diagnosis of Takotsubo, but there are electrocardiogram (ECG) findings that may suggest this diagnosis. The ECG often features QTc prolongation, diffuse T-wave inversions similar to those seen in severe cerebrovascular diseases, ST-elevations mimicking myocardial infarction, as well as deep and diffuse ST depressions [3]. These findings are likely due to an apicobasal intracardiac edema gradient which leads to differential changes in regional action potential duration with dispersion of repolarization from basal to apical sites [3].

While stress alone does not fully explain the development of Takotsubo, there are other known factors that seem to correlate. Kido et al. published a review in 2017 describing 157 reports of drug-induced Takotsubo where almost 70% of cases related to catecholaminergic toxicity. These describe exogenous catecholamines, drugs with known potential adrenergic effect, drugs with adrenergic vasoconstriction properties, and known inhibitors of catecholamine reuptake [4]. Interestingly, Gabriel et al. released an article in 2010 noting a possible association between Takotsubo and treatment with the anti-arrhythmic medication flecainide. They reviewed a series of 12 consecutive patients with Takotsubo, of whom 4 were found to be treated recently with flecainide. They compared this to 1036 separate patients who underwent coronary angiography in the same time period, of which only 7 had received flecainide recently [5]. They proposed that

the negative inotropic effects may play a role in triggering Takotsubo or increasing the degree of LV dysfunction which accompanies Takotsubo. Interestingly, another prior study showed that combining adrenaline and flecainide infusions in healthy volunteers caused prolonged QTc duration, t-wave amplitude flattening, and serum potassium, magnesium, calcium, and phosphate decreases greater than that seen with infusions of adrenaline alone [6]. These are similar ECG changes to those associated with Takotsubo. In our report, we describe a case of Takotsubo in a mentally ill patient after an overdose of flecainide. This highlights the rapid development of Takotsubo shortly after ingestion with a documented supratherapeutic level of flecainide found on the initial blood tests.

Case

A 48 year-old-man with history of pulmonary embolism with embolectomy 3-years prior, and paroxysmal atrial fibrillation treated with flecainide, presented after being found down at home by neighbors for an unknown period of time. Emergency medical services arrived and found him to be awake but altered with slurred speech. They also noted him to be “ice cold, but sweaty.” Family members reported that he had expressed suicidal ideation over the past few days. He was brought to an outside hospital where a 12-lead electrocardiogram (ECG) was obtained which was concerning for possible ST segment elevation myocardial infarction. He was then intubated due to concerns he was not protecting his airway and was flown by helicopter to our facility for potential emergency cardiac catheterization. During transport, he had an episode of bradycardia and was treated with transcutaneous pacing, and he was started on an intravenous epinephrine drip. Our facility performed an ECG which showed a sinusoidal pattern [Fig. 1A]. Rapid “point of care” labs were significant for serum potassium of 6.2 mEq (normal range = 3.3–4.8 mEq/L) and ionized calcium of 10.5 mg/dL (normal range = 4.4–5.2 mg/dL), so he was given 10-units of insulin and 1-amp of 5% dextrose in water. He was emergently taken to cardiac catheterization lab where coronary angiography showed mild non-obstructive disease in the left anterior descending artery and was otherwise normal. The left ventriculogram showed hyperdynamic contraction of the basal segments with akinesis of the apex [Fig. 2]. He was then admitted to the cardiology service where a TTE showed similar findings with the LV having hyperdynamic basal

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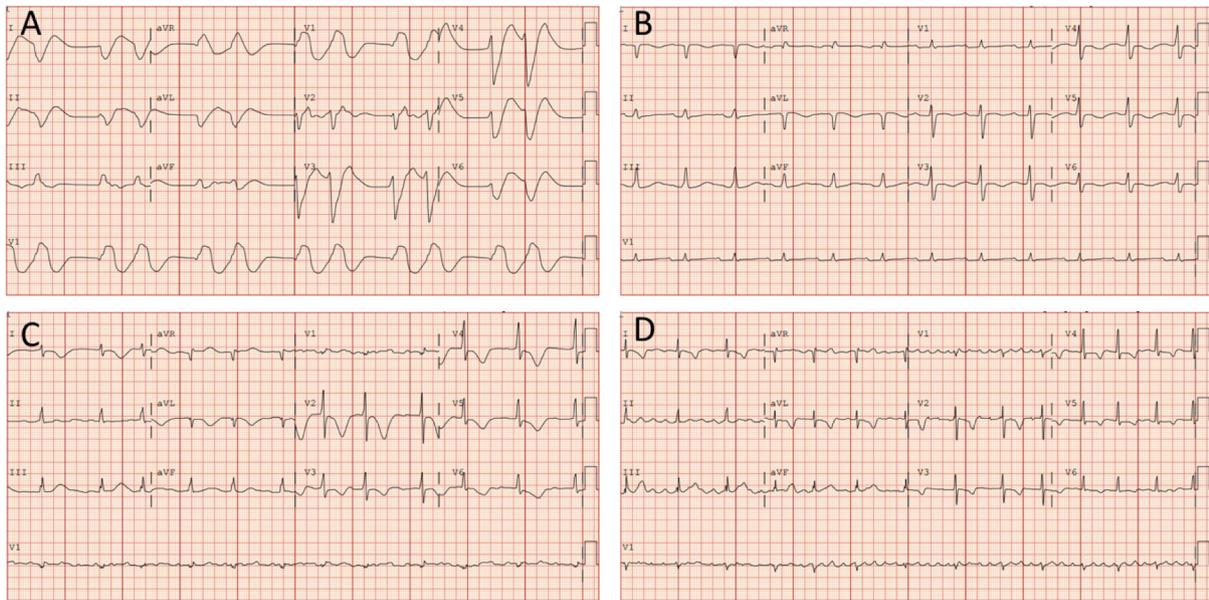


Fig. 1. 12-lead electrocardiograms from admission through discharge. (A) Initial sinusoidal waveforms on admission. (B–C) Hospital day two and three, sinus rhythm with prolonged QTc, ST-depressions, and deep T-wave inversions. (D) Hospital day five, improvement of QTc and T-wave inversions before discharge.

segments and near akinesis of the mid-distal segments extending to the apex. Repeat official labwork revealed potassium of 3.0 mEq and serum calcium of 12.1 mg/dL (normal range = 8.4–10.5), magnesium of 1.8 mEq/L (normal range = 1.6–2.6 mEq/L), normal thyroid function studies, and normal hemoglobin and hematocrit. Troponin-I was mildly elevated and peaked at 0.37 ng/mL (normally <0.03). Urine drug screen was positive for benzodiazepines and opiates (likely used during intubation and transport), negative for ethanol, methanol, and ethylene glycol.

Potassium was repleted, and the wide bigeminal pattern was replaced with sinus mechanism still with intraventricular conduction delay (IVCD) with QRS duration of 200 milliseconds (ms) and prolonged QTc of 601 ms. Given the ECG findings and history, there was concern for potential flecainide toxicity. On the second hospital day, he was successfully extubated and did report taking excessive amounts of home medications, specifically mentioning extra tablets of flecainide. The ECG at this time showed sinus rhythm with IVCD,

narrowed QRS complex at 150 ms, QTc 624 ms, and new broad T-wave inversions (TWI) in leads V3–V6 [Fig. 1B]. A serum flecainide level drawn on the second hospital day was 3.03 µg/mL (therapeutic range 0.20–1.00 µg/mL; toxic range > 1.50 µg/mL). By the third hospital day, repeat ECG showed sinus rhythm with narrowed QRS of 113 ms, QTc length of 626 ms, and extension and worsening of ST changes with diffuse and deep TWI in leads I, aVL, V2–V6, classic for Takotsubo [Fig. 1C]. He was started on metoprolol for rate control of atrial fibrillation and treatment of his cardiomyopathy, and rivaroxaban was continued for anticoagulation. The TWI improved over the following 48 h, and the patient remained stable. His ECG findings improved near the end of his hospitalization [Fig. 1D]. He was then transferred to the inpatient psychiatry unit for evaluation after potential suicide attempt. Subsequent TTE several months later would reveal resolution of apical dyskinesia with normal LV size and function, and ECG showed resolution of TWI and ST changes with normalization of QTc.

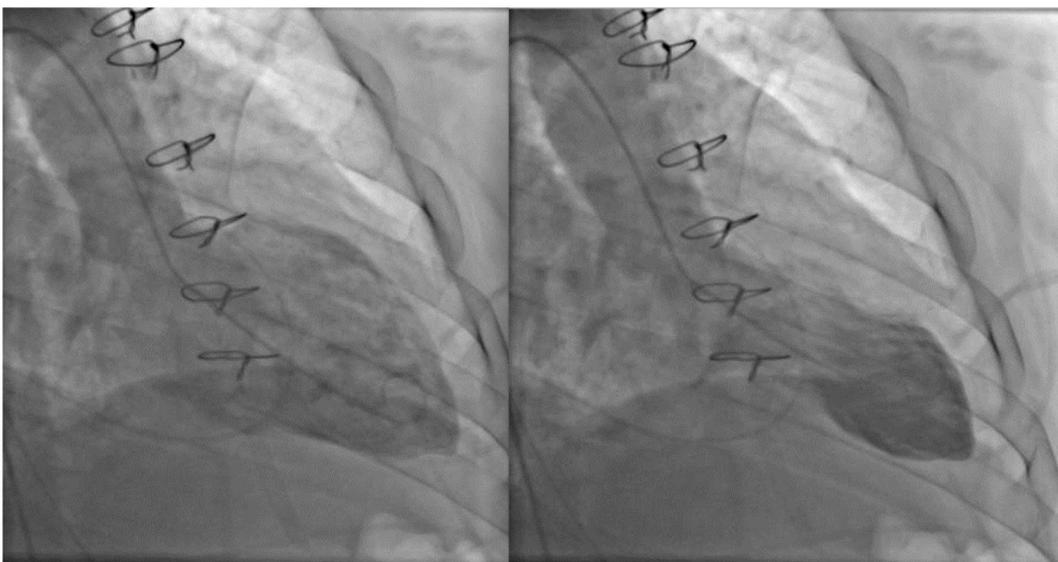


Fig. 2. Left ventriculogram. Basal hyperkinesis with apical ballooning.

Discussion

This case highlights the rapid development of long QT and Takotsubo Cardiomyopathy shortly after a life-threatening flecainide overdose with a serum flecainide level greater than three times the therapeutic dose two days after ingestion. ECGs clearly show progression from flecainide overdose to partial normalization and then on to classic Takotsubo findings. A prior study commented on a potential association between therapeutic doses of flecainide and Takotsubo in a limited number of patients [2]. We believe this is the first case reported in the literature which features an acute overdose of flecainide followed shortly by development of Takotsubo.

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