JAMA Cardiology Clinical Challenge

Syncope in a Young Woman

Catherine E. Lowe, MD; Michael D. Winniford, MD; Tanyanan Tanawuttiwat, MD, MPH

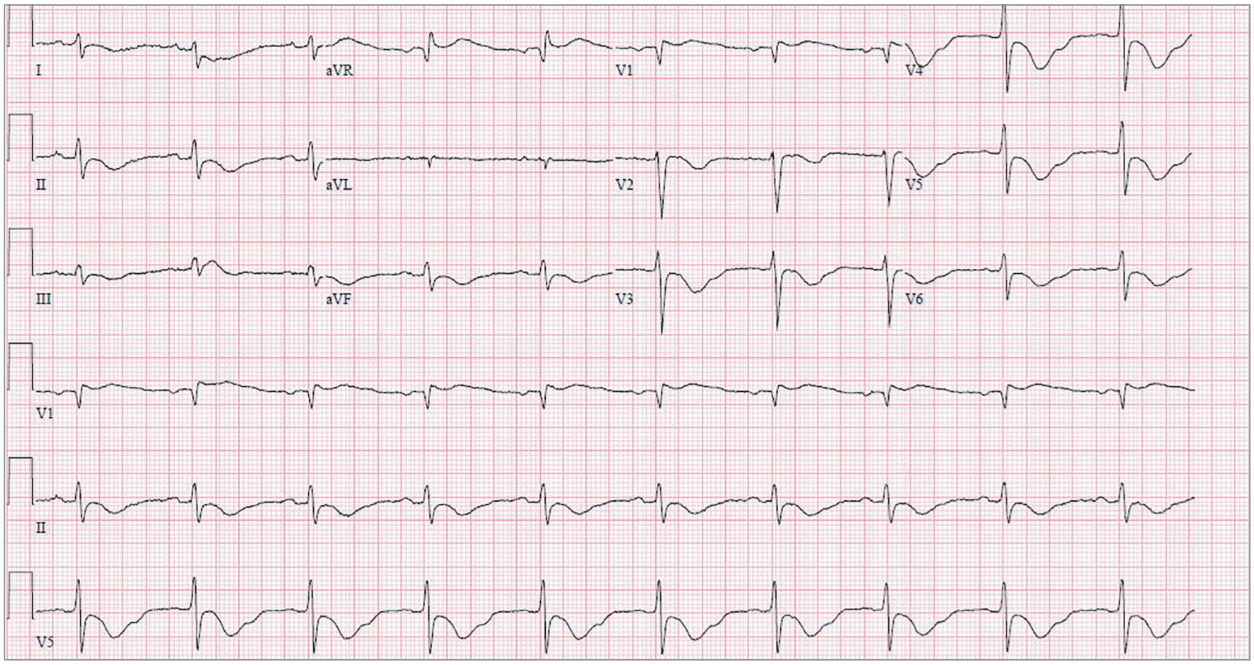

Figure. Initial electrocardiogram at presentation.

A 27-year-old woman with history of heroin use presented with syncope. She was standing and laying out a blanket for her dog before passing out. She denied prodromal symptoms and reported this was her first syncopal episode. She reported a few episodes of dizziness in the couple days prior to presentation but denied chest pain, shortness of breath, palpitations, or the recent use of illicit drugs or new medications. Shortly after arrival at the emergency department, she had a 50-second run of polymorphic ventricular tachycardia. Her vital signs and the results of her physical examination were normal. Troponin levels, thyroid levels, and the results of a complete blood cell count and metabolic panel were all normal. The results of imaging studies, including echocardiography, computed tomography (CT) pulmonary angiography, and brain CT, were also unremarkable. Coronary angiography found no evidence of obstructive coronary disease. The results of the urine toxicology test were negative. An initial electrocardiogram (ECG) at presentation was reviewed (**Figure**).

WHAT WOULD YOU DO NEXT?

A. Start amiodarone infusion therapy

B. Implant an internal implantable cardioverter-defibrillator

C. Perform treadmill stress testing for evaluation of inherited arrhythmias

D. Send blood test for drug levels

Quiz at jamacmelookup.com

Diagnosis

Drug-induced QT prolongation

What to Do Next

D. Send blood test for drug levels

Discussion

The ECG (Figure) showed sinus bradycardia with broad-based, diffuse T-wave inversion and prolonged QT interval (corrected QT interval of 620 milliseconds). The differential diagnosis included ischemia, elevated intracranial pressure, pericarditis, myocarditis, Takotsubo cardiomyopathy, pulmonary embolism, congenital long QT syndromes, and drug-induced QT prolongation. In a patient with a history of substance use, causes of drug-induced prolonged QT in-

terval that should be considered include cocaine use, methadone overdose, and loperamide use. Loperamide is a piperidine derivative and a μ-opioid agonist with antisecretory and antimotility activity. Informally known as "poor man's methadone," loperamide is readily available over the counter and is often used for self-treating opioid withdrawal symptoms or to achieve opioidlike euphoric effects when stronger narcotics are not accessible.[1] Loperamide blocks L-type calcium channels and delayed rectifier potassium channels and has structural similarities to methadone. These properties are postulated to be possible mechanisms of QT interval prolongation and subsequent life-threatening ventricular arrhythmia in overdosed patients.[2,3] Illicit loperamide use has been increasingly reported since the first documented case in 2005.[1] The US Food and Drug Administration (FDA) first issued a warning about the misuse of loperamide in June 2016. The maximum approved daily dosage for adults is 8 mg per day for over-the-counter use and 16 mg per day for prescription use. In September 2019, the FDA approved changes to the product packaging to limit each carton to no more than 48 mg of loperamide.[4] The dosage in the case reports of torsades de pointes (TdP) associated with loperamide overdose varies widely from 60 to 800 mg daily.[3,5] In addition to syncope and ventricular arrhythmia, presenting symptoms may include abdominal cramps, nausea, vomiting, and constipation. ECG findings may include bradycardia, markedly prolonged QT interval, QRS widening, and ventricular arrhythmias.[5] The short-term management of loperamide toxic effects is similar to the treatment of acquired QT prolongation. Unstable patients with TdP require prompt defibrillation and treatment with intravenous magnesium. For stable patients with multiple self-terminating episodes of TdP, supportive treatments include treatment with intravenous magnesium, correction of electrolyte derangements, and interventions to increase heart rate in those with bradycardia, such as overdrive atrial pacing and isoproterenol infusion. Antiarrhythmic medications with prolonged QT effect, including class Ic and III antihiarrhythmics and amiodarone, should be avoided. Loperamide is a lipophilic, highly protein-bound drug (97%) and is unlikely to be eliminated by dialysis.[6] Although the data are limited, intravenous lipid emulsion has been successfully used in the setting of severe cardiac toxic effects in several case reports.[5] After surviving loperamide toxic effects, patients should be screened for an underlying opioid use disorder to reduce the risk of further events.

Patient Outcome

After repeated questioning, the patient eventually disclosed that she had taken 250 two-milligram pills of loperamide. She had no recurrent arrhythmia during observation, and her corrected QT interval gradually shortened to 481 milliseconds. Levels of loperamide and its main metabolite, *N*-desmethyl loperamide, obtained on day 7 after medication use were 5.8 ng/mL (normal level, 5.0 ng/mL) and 41 ng/mL (normal level, 5.0 ng/mL), respectively. She was referred to psychiatry for treatment for substance addiction. Findings from genetic testing were negative for long QT syndromes. She was lost to follow-up and presented again 3 months later with syncope. ECG showed sinus rhythm with a corrected QT interval of 527 milliseconds. The results of the urine toxicology test were negative. Loperamide and *N*-desmethyl loperamide levels were 31 ng/mL and 160 ng/mL, respectively. The patient was warned again about the dangers of loperamide use and referred back to psychiatry for treatment for substance addiction. At 6-month follow-up, she had no recurrent syncope and denied further use of loperamide or other drugs.

ARTICLE INFORMATION

Author Affiliations: Division of Cardiology, Department of Medicine, University of Mississippi Medical Center, Jackson (Lowe, Winniford); Cardiovascular Division, Indiana University Medicine, Indianapolis (Tanawuttiwat).

Corresponding Author: Tanyanan Tanawuttiwat, MD, MPH, Cardiovascular Division, Indiana University Medicine, 1800 N Capital Ave E300B, Indianapolis, IN 46202 (ttanawu@iu.edu).

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