High-dose loperamide abuse–associated ventricular arrhythmias

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Introduction

Loperamide is a synthetic μ-opioid agonist; it is an effective antidiarrheal agent as it inhibits peristalsis and increases rectal tone owing to agonism at intestinal opioid receptors. It was previously thought to have a low potential for abuse owing to its low bioavailability and poor penetration of the central nervous system through the blood–brain barrier.[1,2] There is recent literature that supports loperamide being taken in very large dosages to achieve alleviation of opioid withdrawal symptoms and also to obtain euphoric effects.[3] Massively high sustained doses of loperamide appear to have the potential to exert cardiac effects. In very high and chronic doses, loperamide use is implicated with significant cardiac conduction abnormalities and life-threatening dysrhythmias.[4,5]

We detail a case of a young woman who self-treated her "opiate withdrawal" with chronic massive intake of loperamide and cimetidine abuse and presented with profound electrical conduction disturbances, which resolved after drug cessation.

Case report

A 28-year-old woman was transferred to our hospital for ventricular arrhythmias after presenting to an outside hospital with several episodes of syncope over the past 2 weeks. Her syncopal events occurred mostly at rest and were preceded by palpitations and rapid darkening of her vision. At the outside hospital, her initial electrocardiogram (ECG) showed sinus rhythm with QRS widening and a prolonged corrected QT interval (QTc) of 795 ms, per report. There she was admitted for further evaluation and she had several episodes of ventricular tachycardia with cardiogenic syncope, which all resolved spontaneously or after brief cardiopulmonary resuscitation.

A thorough diagnostic evaluation ensued and was largely normal. Echocardiogram showed normal left ventricular size and systolic function with ejection fraction of 55%–65%. Computed tomography of the chest was unremarkable. Cardiac magnetic resonance imaging (MRI) was normal, without structural abnormalities. MRI of the brain was normal. QRS widening, QTc prolongation, and ventricular arrhythmias persisted throughout her initial course. A lidocaine bolus and amiodarone infusion were used briefly but were discontinued before her eventual transfer to our tertiary care hospital on hospital day 5.

Vital signs upon arrival after transfer were as follows: temperature 98.1°F, heart rate 77 beats per minute (bpm), blood pressure 136/69 mm Hg, respiratory rate 16 breaths per minute, and oxygen saturation 100% on room air. Physical examination was unremarkable except for II/VI systolic heart murmur. ECG showed sinus bradycardia, rate 56 bpm, with first-degree heart block, right axis deviation, and QRS interval of 192 ms and QTc of 642 ms with T wave inversions in lead V2-V4 and T wave flattening in the lateral and inferior leads (Figure 1). Complete blood count was normal other than a white blood cell count of 12.8×10^3; complete metabolic panel was remarkable only for potassium of 3.2 mg/dL. Magnesium and phosphorus were within normal limits.

Shortly after arrival to our hospital she had 2 witnessed syncopal episodes associated with brief myoclonic jerking and ventricular dysrhythmias. The first occurred during 15 seconds of a sustained wide complex rhythm (Figure 2). The second was 58 seconds of a monomorphic wide complex ventricular rhythm with the following rhythm strip and ECG (Figure 3). Each dysrhythmia-associated syncopal episode self-resolved with spontaneous conversion back to sinus rhythm prior to intervention. Because of bradycardia-induced torsade de pointes (Figure 4), an isoproterenol

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KEY TEACHING POINTS

- Loperamide, when taken chronically in large doses, can cause significant conduction abnormalities and ventricular arrhythmias that are reversible upon discontinuation of the drug.
- Isoproterenol may serve as a useful adjunct for preventing loperamide-induced ventricular arrhythmias, particularly torsades de pointes.
- Familiarity with and recognition of the dangers of loperamide abuse may preclude unnecessary diagnostics and invasive procedures.

infusion was initiated soon after and titrated to a goal heart rate of 90 bpm, and a transvenous pacemaker was also inserted in the event she should require overdrive pacing.

The patient denied any history of prior cardiac disease or syncope. She denied any current illicit drug or alcohol abuse. There was no family history of sudden or unexplained death. She reported a remote history of hydromorphone abuse. She had been taking her current home medications, including loperamide, cimetidine, and gabapentin, since discontinuing hydromorphone, after reading on the Internet that they could ease opioid withdrawal symptoms. It was then that she divulged her chronic, massive intake of loperamide and cimetidine when further questioned. In fact, for the past several months on a daily basis she had been routinely ingesting 400–600 mg of loperamide (in the form of 2 mg tablets) and 2000 mg of cimetidine (in form of 200 mg tablets). Moreover, she had still been ingesting approximately 100 tablets of loperamide and 10 tablets of cimetidine daily from her private stock of medication during her first hospitalization, unbeknownst to the medical staff. Once this intake was recognized at our facility, she was educated about the dangers of this practice and the patient subsequently discontinued loperamide and cimetidine intake.

The drug-induced cardiac effects persisted for several days but slowly improved. Initial trials to wean isoproterenol were unsuccessful, resulting in slowing of the heart rate, widening of the QTc, and ventricular ectopy. Isoproterenol was continued for 5 days to maintain an increased heart rate and effectively prevent significant ventricular ectopy. The QTc, measured while isoproterenol infusion was held, slowly narrowed over the course of her 11-day stay in our intensive care unit. The narrowest QTc measured was 492 ms while at rest. Echocardiography was repeated and was essentially normal. She was predominantly bradycardic after discontinuation of the isoproterenol, with a heart rate (bpm) ranging from the 40s to the 70s. Genetic testing for long QT syndrome was to be considered at a later time, but this condition was thought less likely given her steady improvement. She was started on nadolol 40 mg per os daily, which was tolerated well. Final ECG prior to discharge showed normal QRS interval and QTc 516 ms (Figure 5). She was discharged home on hospital day 16 and was doing well upon phone contact several days later.

Serum concentration of loperamide, drawn shortly after her transfer to our facility, was 83.2 ng/mL (therapeutic range, 0.24–3.1 ng/mL) and cimetidine was 6 μg /mL (therapeutic range, 0.5–1.5 μg/mL). Ultraperformance liquid chromatography–time-of-flight mass spectrometry of the urine only showed the presence of cimetidine, morphine,

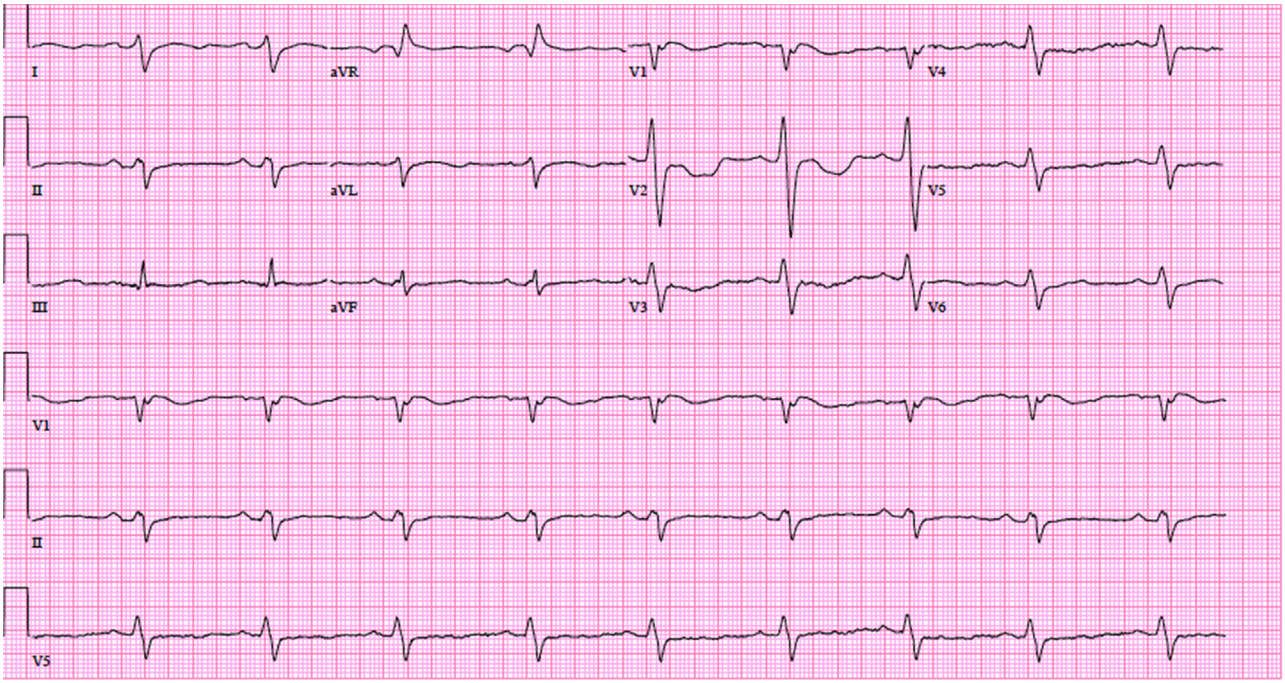

Figure 1 Patient's initial electrocardiogram after transfer, hospital day 5, PR 210 ms, QRS 192 ms, QTc 642 ms.

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