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

KEYWORDS Loperamide; Cimetidine; Ventricular tachycardia; Isoproterenol; Opiate withdrawal; External pacemaker
(Heart Rhythm Case Reports 2016;2:232–236)

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http://dx.doi.org/10.1016/j.hrcr.2016.01.002

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,

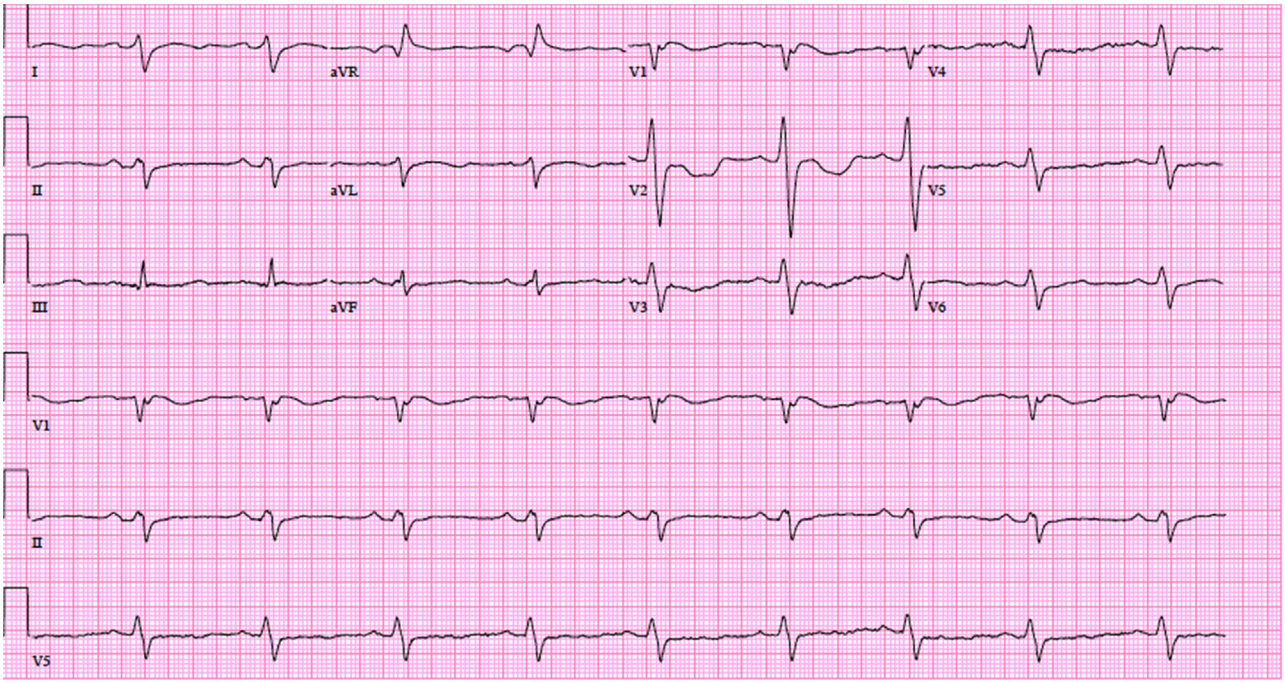

Figure 1 Patient's initial electrocardiogram after transfer, hospital day 5, PR 210 ms, QRS 192 ms, QTc 642 ms.

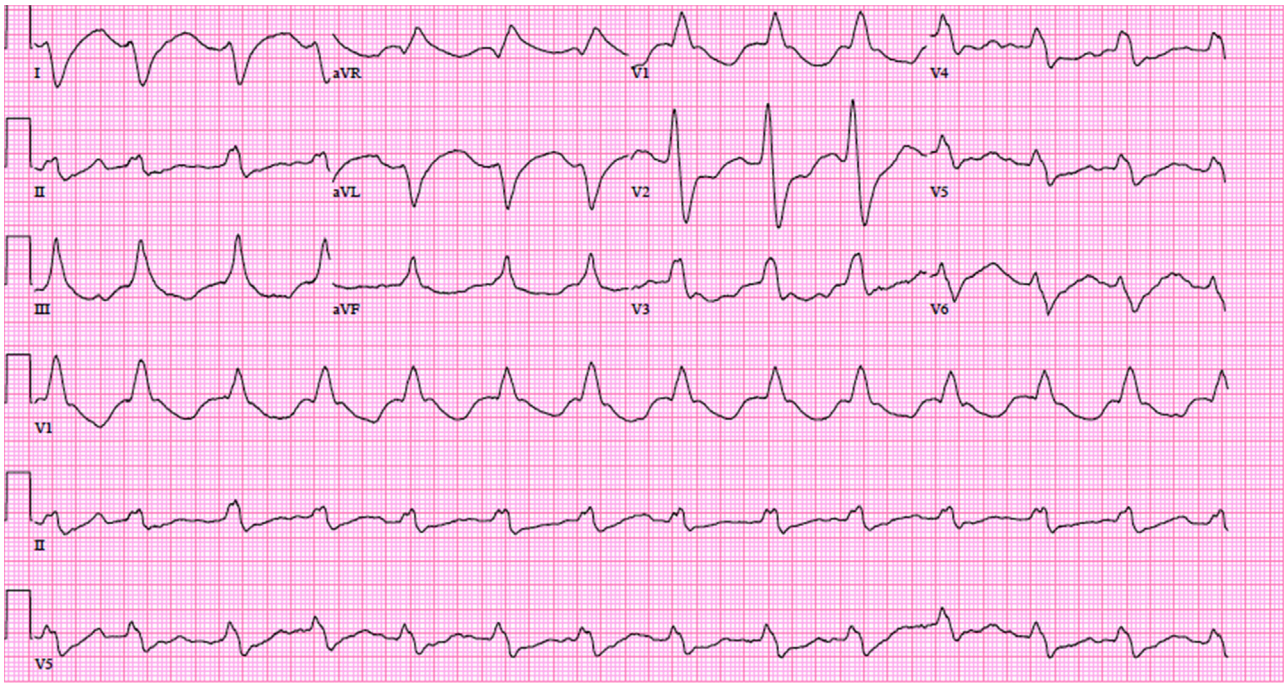

Figure 2 Wide complex arrhythmia during initial syncopal episode.

loperamide, and its metabolite dimethyl-loperamide. The presence of morphine was consistent with the morphine she was administered during her first hospital stay. Methadone, amphetamines, and cocaine were not detected.

Discussion

Marraffa et al[4] recently reported a small case series of 5 patients, detailing high-dose chronic loperamide abuse with ECG changes, namely QRS and QTc prolongation, and a variety of ventricular dysrhythmogenic events. Similar to our case, the 5 patients within this case series all had QRS widening and QTc prolongation, which improved or normalized with discontinuation of loperamide. T wave inversions across the precordial leads was another commonality seen in several of these cases. The mechanism of the cardiac conduction defects is not well understood, but there are simulated model data that suggest loperamide is a human ether-a-go-go gene (*HERG*) coded rectifier potassium ion current channel inhibitor.[6] Methadone, another opioid, is

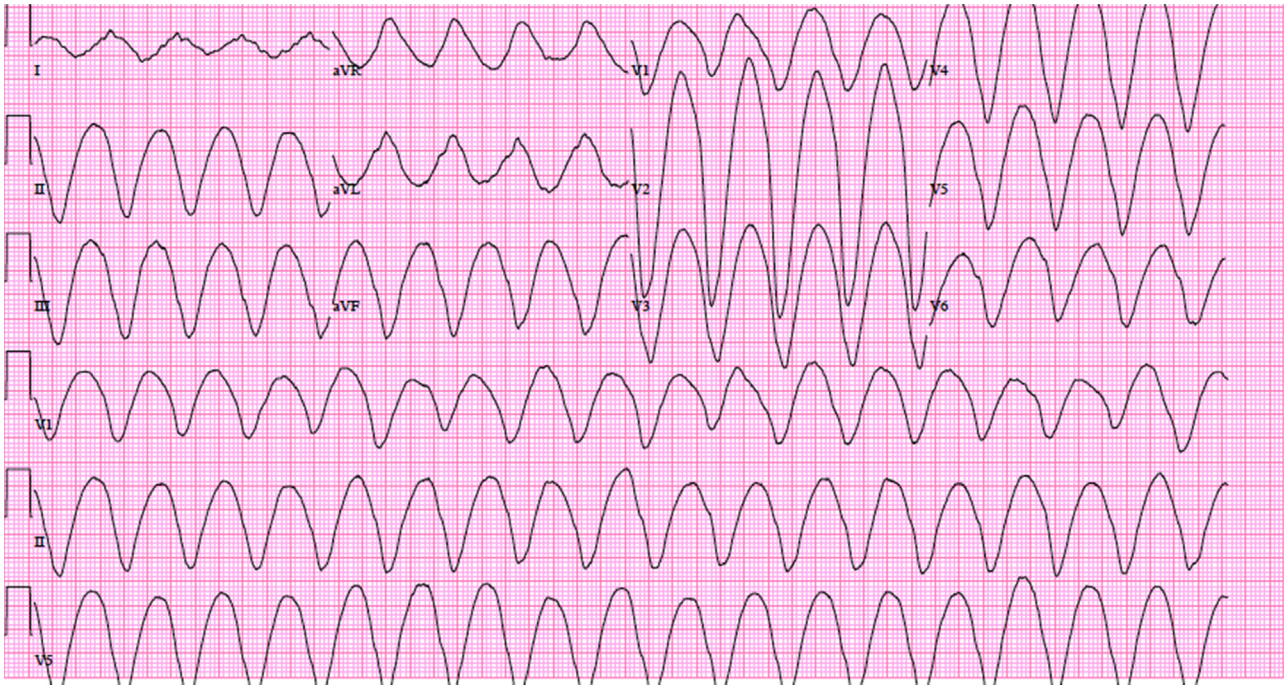

Figure 3 Wide complex tachycardia during second syncopal episode.

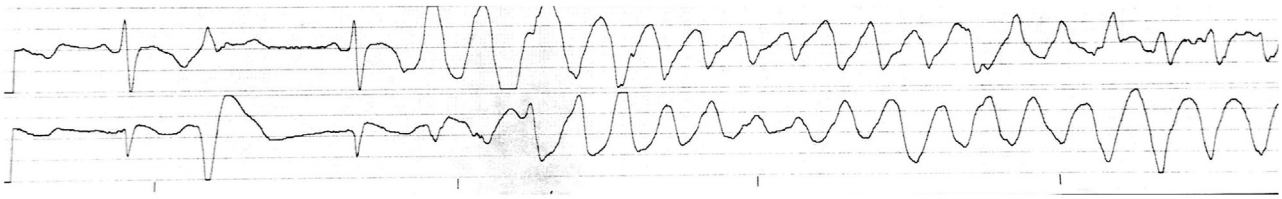

Figure 4 Bradycardia-induced torsades de pointes.

well known to have drug-induced QT prolongation through inhibition of the rapidly activating component of the delayed potassium ion current.[7] The widened QRS interval would suggest some element of sodium channel blockade, but there is little known about the effects of loperamide on sodium channels. In our patient, we were not able to exclude an underlying channelopathy, but the discontinuation of loperamide and supportive care led to gradual but dramatic improvement in QRS and QT intervals and abatement of ventricular arrhythmias.

Loperamide is primarily metabolized by cytochrome p450 (CYP) 3A4 and CYP2C8 and it is also a p-glycoprotein efflux transporter substrate.[8,9] The therapeutic pharmacokinetic half-life of loperamide is approximately 9–14 hours.[10] Extremely high doses may saturate the metabolic pathway and the excretory efflux transport, allowing it to exert central nervous system and other physiological effects. The prolonged effects of loperamide as demonstrated in this case are not unexpected in terms of pharmacokinetic principles. The half-life can be quite prolonged in supratherapeutic dosages.[5,11] Eggleston et al[5] reported a half-life of 34.8 hours in a case of QRS and QTc prolongation with ventricular dysrhythmia. The decreased intestinal motility seen with loperamide may also contribute to delayed and ongoing absorption. In addition to increased body burden of absorbed drug from chronic abuse, the patient theoretically may have had ongoing absorption from gastrointestinal contents from recent ingestions, given the delayed gastrointestinal motility expected with chronic loperamide use.

The concurrent use of cimetidine is a unique aspect to this case not previously reported. Cimetidine, a histamine type 2 receptor antagonist, is also a well-known CYP3A inhibitor.[12] It is likely that the intent of simultaneous use of cimetidine, another affordable over-the-counter product, is to take advantage of CYP inhibition and slow the metabolism of loperamide, lending to higher concentrations and desired effect. Cimetidine is a p-glycoprotein substrate but not a known inhibitor to cause increased loperamide serum concentrations by blockade of efflux transport.[8] It is not certain, but it is unlikely that cimetidine was directly responsible for the cardiac effects seen in this case. It has not been a noted co-ingestant in other reported chronic loperamide overdose cases with similar features and is not known to have such effects in isolated overdose. There are some sparse scientific reports detailing sinus arrest and hypotension associated with intravenous cimetidine use, especially with rapid bolus, but it has not been described with oral administration.[13–15]

Delayed recognition of excessive loperamide intake appears to be a common feature in our and other case reports

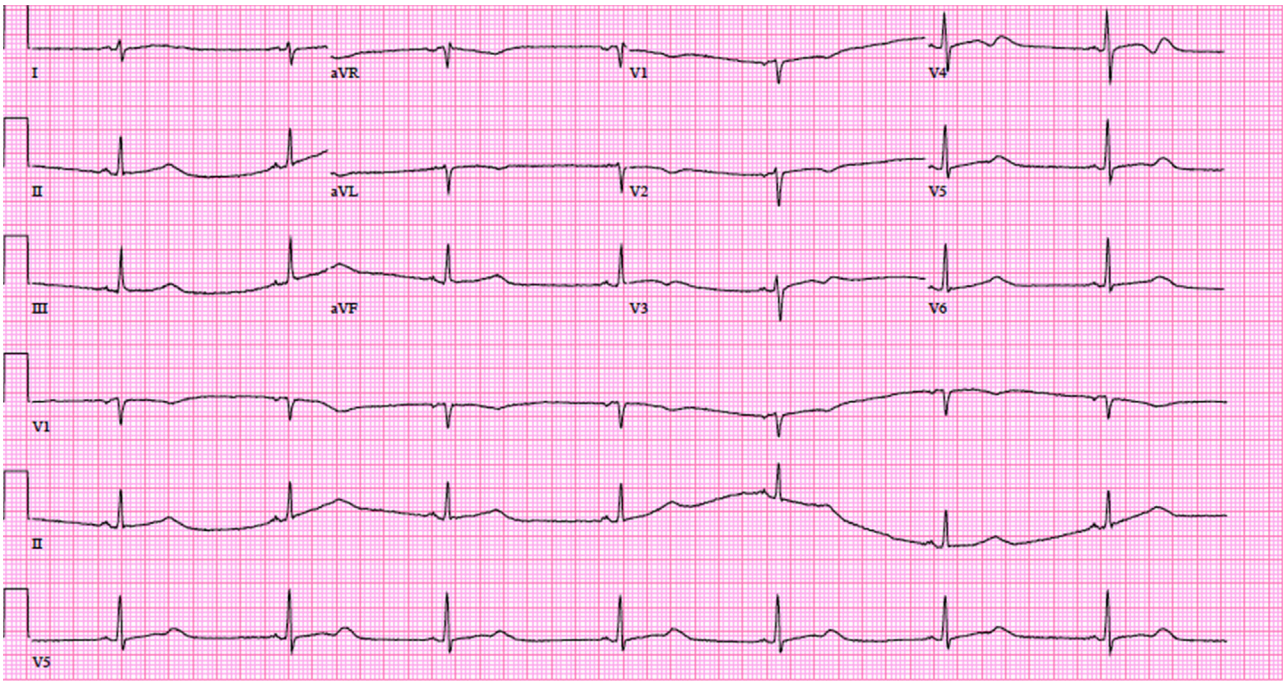

Figure 5 Final electrocardiogram before discharge, hospital day 15, QRS 80 ms, QTc 516 ms.

of loperamide-associated cardiac conduction abnormalities.[4] This appears to be a product of patient discretion and lack of physician awareness regarding the potential danger of this over-the-counter product.

Conclusion

This case details the very serious and potentially life-threatening cardiac dysrhythmias that are associated with both chronic and very high doses of loperamide. Loperamide may not be as innocuous as once thought, when purposefully abused in chronic, high quantities. Isoproterenol infusion was very successful in eliminating ventricular arrhythmias in this setting. Loperamide overdose should be considered, when case appropriate, as a potential cause in similar cases of significant cardiac syncope and cardiac conduction disturbances with prolonged QRS and QTc intervals. Given the ubiquity of loperamide and the epidemic of opioid abuse, this may represent a growing problem. The number of new cases warrants further investigation and physician provider awareness.

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