Electrocardiographic Abnormalities, Malignant Ventricular Arrhythmias, and Cardiomyopathy Associated With Loperamide Abuse

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Electrocardiographic Abnormalities Associated With Loperamide Abuse. A 20-year-old man presented with recurrent syncope and abnormal electrocardiogram (ECG). His evaluation revealed a prolonged QT interval >600 milliseconds, witnessed torsades de pointes (TdP), and dilated cardiomyopathy. At his initial admission, an ICD was implanted and atrial pacing at 80 beats per minute suppressed ventricular arrhythmias. The patient was readmitted with device infection and recurrent TdP leading to intubation. This led to the discovery of a hitherto unrevealed loperamide abuse and his cardiac arrhythmias and LV dysfunction were determined to be related to large doses of loperamide. Following abstinence, his ejection fraction and ECG returned to normal. (J Cardiovasc Electrophysiol, Vol. 27, pp. 1230-1233, October 2016)

Implantable Cardioverter Defibrillator (ICD), Loperamide, Narcotic withdrawal, QT prolongation, Torsades de Pointes (TdP)

Introduction

Loperamide is a widely available over-the-counter antidiarrheal agent that acts as a peripheral µ-opioid receptor agonist. Over the last decade an online movement has emerged using the drug for opioid withdrawal symptoms or recreational abuse. We report the case of a young man presenting with recurrent syncope, abnormal electrocardiogram (ECG), and life-threatening ventricular arrhythmias due to loperamide abuse.

Case Presentation

A 20-year-old male with a remote history of intravenous drug use presented to our emergency department after 2 episodes of syncope while ambulating at home. Over the previous 4 months, the patient reported multiple episodes of palpitations, shortness of breath, and near syncope. His family history was negative for sudden death. The physical examination was normal, but the admission 12-lead ECG was grossly abnormal with broad QRS complexes and QT prolongation (Fig. 1). A standard urine drug screen was negative. On day 2 of admission, he had syncope with telemetry revealing torsades de pointes (TdP) that degenerated to ventricular fibrillation (VF) (Fig. 2). Telemetry recordings showed spontaneous conversion of VF after 45 seconds, sinus bradycardia with a heart rate in the low 50 beats per minute (bpm) range, frequent premature ventricular contractions (PVCs) and postpause QT prolongation. An intravenous isoproterenol infusion was initiated resulting in an increased sinus rate to about 80 bpm and suppression of ventricular ectopy. A cardiac magnetic resonance imaging (MRI) revealed dilated cardiomyopathy with a left ventricular ejection fraction (EF) of 45%. The right ventricle was normal. The 2D echocardiogram also revealed mild global hypokinesis of the left ventricle and an estimated EF of 40–45%. The patient was suspected to have a genetic defect accounting for his abnormal ECG and VF episode. A dual chamber ICD was implanted with the lower atrial pacing rate of 80 bpm per minute, which shortened the QT interval to 500 milliseconds, and completely suppressed ventricular arrhythmias (Fig. 3). He was released home on metoprolol succinate 12.5 mg daily with the recommendation for genetic testing as an outpatient.

Three weeks later the patient was readmitted with a device pocket infection and underwent ICD system removal and antibiotic treatment. There were no arrhythmias detected on the ICD interrogation. With discontinuation of atrial pacing, the sinus rate was observed to be in the mid 50 bpm range and QTc 600 milliseconds. On day 4 of admission, the patient had multiple episodes of sustained TdP events that required 5 external defibrillations. He was intubated and sedated. An isoproterenol infusion was started with control of VF events and reimplantation of a dual chamber ICD from the right infraclavicular region was performed on day 7 of admission. Atrial pacing at 80 bpm again suppressed ventricular arrhythmias and isoproterenol was discontinued.

Upon extubation on day 9, the patient developed opioid withdrawal symptoms and admitted to use of high doses of loperamide daily over the last year. He started this habit to prevent withdrawal symptoms when he quit heroin. He took up to 288 mg loperamide daily (2 bottles of 2-mg tablets) and continued the habit in-hospital assisted by a friend without the knowledge of the staff. The last loperamide tablet taken was reported to be on the morning of the day of intubation.
Figure 1. Presenting ECG. Grossly abnormal ECG with PR interval prolonged to 320 milliseconds, QRS duration of 200 milliseconds, and QTc of 600 milliseconds. For a high quality, full color version of this figure, please see Journal of Cardiovascular Electrophysiology’s website: www.wileyonlinelibrary.com/journal/jce

Figure 2. Torsade de pointes. Telemetry recording showing onset of torsade de pointes.

Figure 3. Atrial pacing at 80 bpm. QRS duration is prolonged to 160 milliseconds and QTc is 500 milliseconds. For a high quality, full color version of this figure, please see Journal of Cardiovascular Electrophysiology’s website: www.wileyonlinelibrary.com/journal/jce
The patient underwent inpatient and outpatient drug rehabilitation. At 6 weeks, the follow-up ECG revealed atrial pacing at 80 bpm and normal intervals (Fig. 4), and repeat 2D-echocardiogram showed normalization of EF to 55%.

**Discussion**

The temporal relationship of ECG changes and ventricular arrhythmias to loperamide use in our patient’s case suggests this to be the likely etiology of his prolonged QTc, QRS prolongation, and episodes of TdP. This became evident during the second hospitalization when the patient no longer had access to loperamide while intubated. There was near normalization of ECG changes and resolution of ventricular arrhythmias a few days after discontinuation of loperamide. The half-life of loperamide is approximately 9–13 hours. The patient continued to have a detectable loperamide level in the therapeutic range 6 days after his known last ingestion, suggesting very high drug levels during the abuse. Levels were not evaluated earlier since there was no reason to suspect this etiology. We could not identify any other potential etiology, including inpatient medications that could account for the patient’s presentation.

Loperamide is a peripherally acting µ-opioid receptor agonist that acts on sites in the large intestine in an effort to slow intestinal peristalsis, decrease fluid and electrolyte loss, and inhibit secretion. FDA-approved in 1976, clinicians have long used it as an over-the-counter means of alleviating diarrhea. At the recommended maximum daily dose of 16 mg/day, loperamide’s effects appear to be limited to the gut with minimal penetration of the blood–brain barrier. It is thought to be devoid of abuse potential owing to considerable first-pass metabolism and poor blood–brain barrier penetration because of P-glycoprotein efflux pump. Saturation of P-glycoprotein efflux transporters explains the euphoric effects seen at high doses and the consequent abuse potential.

With a potential for euphoric effects at high doses, easy accessibility and low expense, the use of loperamide as a remedy for opioid withdrawal and its recreational use as an opioid substitute is widely discussed in online drug forums. Indeed, in 1 observational study of web-based trends of the opioid substitute is widely discussed in online drug forums. Indeed, in 1 observational study of web-based trends of the opioid substitute is widely discussed in online drug forums.

There is a paucity of electrophysiology literature describing the cardiac toxicity associated with loperamide abuse. A few case reports available are primarily in the toxicology literature. Marraffa et al. were among the first to report the association observed between loperamide abuse and cardiac conduction disturbances: they described 5 individual cases observed at various institutions in which patients presented with a life-threatening cardiac arrhythmia temporally related to loperamide abuse. One of the patients experienced a second life-threatening arrhythmia after resuming loperamide abuse following discharge from the hospital. Loperamide levels were obtained in most of these patients and found to be at least 1 order of magnitude greater than therapeutic concentrations. Furthermore, discontinuation of this medication resulted in a complete resolution of the ECG changes seen on admission. At his 6-week follow-up with abstinence from loperamide, the patient’s ECG remained normal and his left ventricular dysfunction resolved completely.

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Figure 4. ECG 6 weeks after discontinuation of loperamide showing normalization of intervals. The rhythm is atrial paced at 80 bpm, PR interval 160 milliseconds, QRS duration 90 milliseconds, and QTc 440 milliseconds. For a high quality, full color version of this figure, please see Journal of Cardiovascular Electrophysiology’s website: www.wileyonlinelibrary.com/journal/jce
A dynamic public registry for long QT drugs (http://www.crediblemeds.org/everyone/composite-list-allqtdrugs) has recently categorized loperamide as a QT prolonging drug with a conditional risk of TdP. In comparison, methadone, a central-acting μ-opioid receptor agonist with structural similarities to loperamide, is classified as high risk for TdP. Methadone has been associated with dose-dependent QT interval prolongation and TdP. In addition, the United States Food and Drug Administration has recently released a warning about serious cardiac arrhythmias, including cardiac arrest, associated with loperamide abuse.

The frequency with which cardiac electrophysiological abnormalities occur in patients abusing loperamide is unknown. It could be patient specific and it is possible that susceptible patients may have underlying genetic variations that become manifest when exposed to high doses of the drug. The exact mechanism whereby loperamide leads to these cardiac conduction disturbances at supratherapeutic doses is unclear. Marraffa et al. propose that high drug concentrations of loperamide block I_Kr channels and I_Na channels, leading to QT prolongation and QRS prolongation, respectively. Spinner et al. recognize the structural similarity that exists between loperamide and another piperidine derivative known to cause cardiac arrhythmia: haloperidol. QTc prolongation related to other synthetic opioids such as methadone has been recognized to be due to blockade of the cardiac I_Kr channels, and due to structural homology with methadone, it is speculated that loperamide also blocks I_Kr.

**Conclusion**

This case illustrates the evolving cardiac risks related to routinely used over-the-counter medications. Patients often do not reveal such information during encounters and clinicians need awareness to be specific in interviewing for etiology of unusual presentations.

**References**