Loperamide overdose causing torsades de pointes and requiring Impella temporary mechanical support: a case report

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Background
Loperamide is a widely available oral μ-opioid receptor agonist, and loperamide abuse is increasing by those seeking intoxication. Loperamide has potent QTc-prolonging properties, placing patients at risk for ventricular arrhythmias and sudden cardiac death.

Case summary
A 23-year-old woman was found to be in pulseless ventricular fibrillation with a QTc of 554 ms and received multiple defibrillations and IV lidocaine. Her toxicology studies were negative. She subsequently experienced multiple episodes of torsades de pointes and was found to be in cardiogenic shock with a left ventricular ejection fraction of 5%. Following multiple defibrillations, an Impella® mechanical circulatory support device was placed, and she was given IV magnesium and IV lidocaine. After mechanical circulatory support was withdrawn, she experienced major bleeding and was found to have a deep vein thrombosis, bilateral radial artery thrombosis, and multiple pulmonary embolisms in the setting of heparin-induced thrombocytopenia. After stabilizing, she admitted to taking 80 tablets of loperamide 2 mg in pursuit of euphoria.

Discussion
Loperamide is an increasingly popular agent of abuse. Loperamide-associated ventricular arrhythmias are rare with normal doses but more common with high doses, chronic ingestion, or interacting medications. Loperamide cardiotoxicity may be prolonged due to a long half-life and accumulation. Loperamide abuse may be under-recognized, leading to delays in treatment. Intravenous fluids, magnesium supplementation, chronotropes, transcutaneous or transvenous pacing, and defibrillation may be helpful in mitigating loperamide-associated polymorphic ventricular tachycardia. Clinicians should monitor for drug interactions in patients taking loperamide and screen for electrocardiographic abnormalities in those taking chronic or high-dose loperamide.

Keywords
Loperamide • Ventricular arrhythmia • Torsades de pointes • QTc prolongation • Overdose • Case report

Learning points
• Loperamide is an increasingly popular agent of abuse and can cause life-threatening ventricular arrhythmias with high doses or interacting medications.
• Loperamide-associated ventricular arrhythmias are often under-recognized.
• Loperamide cardiotoxicity may be prolonged due to a long half-life and accumulation.
Introduction

Loperamide is a μ-opioid receptor agonist that is 50 times more potent than morphine. Because loperamide is a P-glycoprotein substrate, efflux pumps in enterocytes and the central nervous system lead to low bioavailability and poor penetration through the blood–brain barrier. As a result, loperamide does not cause analgesia, euphoria, or respiratory depression at usual doses (≤16 mg in 24 h) and was historically viewed as ‘free of abuse potential’.1–7 Since the 1980s, loperamide has been classified as an over-the-counter product, and few incidents of intentional abuse have been reported to poison control centres through 2007.1,4,8

Between 2009 and 2015, the number of calls to poison control centres regarding intentional loperamide ingestions more than doubled, and Google searches for ‘loperamide high’ and ‘loperamide centres regarding intentional loperamide ingestions’ steadily increased since 2011.1 Other analyses of online drug abuse forums note increased discussion of loperamide’s euphoric effects and potential for managing opiate withdrawal.7,9,10 About 18% of loperamide-related misuse/abuse cases from poison control centres involve cardiotoxicity, including tachycardia, bradycardia, ventricular arrhythmias, and cardiac arrest.1 Other investigations have observed increased loperamide-related activity through both the FDA Adverse Event Reporting System and poison control centres.4,5,9 Online drug abuse forums have endorsed using ‘boos ters’ [including black pepper (piperine), cimetidine, and quinine] to increase bioavailability and augment loperamide’s euphoric effects.1

We describe a case report of a 23-year-old woman presenting with loperamide overdose and cardiac arrest requiring mechanical circulatory support.

Timeline

Initial presentation
• A 23-year-old woman was found with pulseless cardiac arrest and received bystander cardiopulmonary resuscitation (CPR).
• Rhythm identified as pulseless ventricular fibrillation arrest. Received two defibrillations and intravenous lidocaine by emergency responders.
• QTc was 554 ms with a cove-like ST-elevation pattern upon hospital arrival and toxicology studies were negative.

Next several days
• She was intubated and targeted temperature management (TTM) was initiated to preserve neurological function; dobutamine was initiated after an echocardiogram revealed left ventricular ejection fraction (LVEF) 10–15%, consistent with a stress-induced cardiomyopathy.
• After completion of 24 h of TTM, she was extubated. She was then found to be in torsades de pointes (TdP) with QTc 613 ms requiring three electrical cardioversions.
• She developed cardiogenic shock (blood pressure (BP) 84/34 mmHg, heart rate 109 b.p.m.). Cardiogenic shock was felt to be secondary to recurrent, pulseless, electrical instability from TdP. A bedside echocardiogram demonstrated worsening left ventricular hypokinesis with an LVEF of 5–10%, likely related to worsening stress-induced cardiomyopathy. She was intolerant of increased inotropes due to recurrent arrhythmias, which persisted despite lidocaine administration. Amiodarone was avoided given concerns of further QTc-prolongation.
• Given the clinical impression of cardiogenic shock and recurrent pulseless arrhythmias, the transferring facility placed an Impella® 2.5 mechanical circulatory support device via the right femoral artery. She was then transferred to University of North Carolina Medical Center (UNCMC) for further management. In transfer, new

Case presentation

A 23-year-old woman with no known past medical history was found in pulseless ventricular fibrillation arrest and received cardiopulmonary resuscitation (CPR), two defibrillations, and intravenous lidocaine by emergency responders. Upon hospital arrival, her QTc was 554 ms with a cove-like ST-elevation pattern (Figure 1). Toxicology studies were negative.

The patient underwent targeted temperature management (TTM) to preserve neurologic function. An echocardiogram revealed a left ventricular ejection fraction (LVEF) of 10–15% with diffuse hypokinesis and a hypercontractile apex, most consistent with a stress-induced cardiomyopathy, and she was initiated on dobutamine. After completion of TTM and extubation, she experienced recurrent torsades de pointes (TdP) (QTc 613 ms) requiring three electrical cardioversions (Figure 2).

Following these cardioversions, she developed worsening hypotension and was determined by the transferring facility to be in cardiogenic shock [blood pressure (BP) 84/34 mmHg, heart rate 109 b.p.m.]. Cardiogenic shock was felt to be secondary to recurrent, pulseless, electrical instability from TdP. A bedside echocardiogram demonstrated worsening left ventricular hypokinesis with an LVEF of 5–10%, likely related to worsening stress-induced cardiomyopathy. She was intolerant of increased inotropes due to recurrent arrhythmias, which persisted despite lidocaine administration. Amiodarone was avoided given concerns of further QTc-prolongation.

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- An Impella® 2.5 mechanical circulatory support device was placed percutaneously due to haemodynamic instability at the transferring centre.
- Transfer to tertiary academic medical centre
- TdP was managed with IV magnesium boluses and increased lidocaine infusion.
- Impella® device removed as she became haemodynamically stable.
- Two spontaneous haemorrhages occurred at the right femoral arteriography site and led to decreased haemoglobin (nadir of 4.1 g/dL).
- She was found to have a large subcapsular liver haematoma, right common iliac vein deep vein thrombosis, bilateral radial artery thrombosis, and multiple small pulmonary embolisms.
- Argatroban was initiated for heparin-induced thrombocytopenia with thrombosis, and patient was transitioned to dabigatran for discharge.
- She admitted to ingesting 80 tablets of loperamide 2 mg (160 mg total) in pursuit of intoxication.
information obtained by interviewing the patient’s significant other indicated she had acutely ingested high doses of loperamide, in addition to previous chronic loperamide ingestion.

Upon arrival to UNCMC, persistent episodes of TdP were managed with intravenous magnesium boluses and increased lidocaine infusion rates. Overdrive pacing with a temporary pacemaker was
considered at this time, but her rhythm subsequently stabilized. Her QTc shortened over the subsequent days, and her BP normalized as she remained free of arrhythmias. Her mechanical circulatory support and lidocaine infusion were subsequently weaned.

Following removal of the Impella, she experienced two spontaneous haemorrhages at the right femoral arteriotomy site. The second episode was managed by balloon tamponade. After apparent haemostasis and angiographic resolution of her bleed, she developed worsening hypotension. Her haemoglobin acutely decreased to a nadir of 4.1 g/dL. A computed tomography scan demonstrated a large subcapsular liver haematoma and a right common iliac vein deep vein thrombosis (DVT). She was subsequently noted to have bilateral radial artery thrombosis. Argatroban was started due to concern for heparin-induced thrombocytopenia with thrombosis (HITT). Her platelet factor 4 antibody was positive, and a ventilation/perfusion scan found multiple small pulmonary embolisms (PEs).

Her oxygen requirement and thrombocytopenia improved with argatroban. After extubation, she admitted to taking up to 80 tablets of loperamide 2 mg (160 mg total) at a time in pursuit of intoxication. She had been practicing this behaviour for years after discovering it on the Internet and was unaware of potential complications. She was discharged on dabigatran for multiple PEs and DVT in the context of HITT.

In follow-up, the patient appeared well and had normalization of laboratory values, electrocardiogram, and LVEF (Figure 3).

Discussion

Loperamide has been identified as a likely inhibitor of both the human ether-a-go-go-related gene (hERG) potassium channel K$_{11.1}$ and the cardiac sodium channel Na$_{1.5}$. The hERG potassium channel underlies the delayed rectifier potassium current (I$_{Kr}$), and is the most common potassium channel associated with drug-induced QT-prolongation. Loperamide shares several structural similarities with and demonstrates comparable hERG-channel- affinity to terfenadine and cisapride, medications with established QTc-prolonging risks. Loperamide’s inhibition of the Na$_{1.5}$ channel may potentiate QRS widening, a side effect not shared with terfenadine or cisapride.

Loperamide also inhibits L-type Ca$^{2+}$ channels, which may further increase action potential duration.

Loperamide’s toxicity may be enhanced by interacting medications (Table 1). Since loperamide is primarily metabolized by CYP2C8 and CYP3A4 and is a P-glycoprotein substrate, medications inhibiting these proteins may result in clinically significant loperamide interactions; clinically significant medication interactions involving CYP 2B6 and CYP 2D6 have not been reported.

Management of loperamide-associated polymorphic ventricular tachycardia (VT) remains largely supportive. Loperamide and interacting medications should be immediately discontinued when toxicity is suspected. Intravenous fluids, magnesium, chronotropes, transcutaneous or transvenous pacing, and defibrillation may be helpful in mitigating polymorphic VT. Minimal data exist for using antiarrhythmic medications to manage loperamide-induced arrhythmias or using naloxone for loperamide-induced respiratory depression. Activated charcoal is not expected to be helpful in cases of chronic or acute loperamide use. Due to high protein binding, haemodialysis is unlikely to remove excess loperamide from circulation. Mechanical circulatory support may be considered for refractory cardiogenic shock, haemodynamic compromise, or recurrent cardiac arrest. Importantly, routine opiate screens do not include loperamide and...
Loperamide-associated torsades de pointes

Table 1  Loperamide medication interactions that may increase loperamide toxicity

| Medication       | Proposed mechanism of interaction |
|------------------|-----------------------------------|
| Cimetidine       | CYP3A4 inhibition                 |
| Clarithromycin   | CYP3A4 inhibition; P-glycoprotein inhibition |
| Erythromycin     | CYP3A4 inhibition; P-glycoprotein inhibition |
| Gemfibrozil      | CYP2C8 inhibition                 |
| Itraconazole     | CYP3A4 inhibition; P-glycoprotein inhibition |
| Ketoconazole     | CYP3A4 inhibition; CYP2C8 inhibition; P-glycoprotein inhibition |
| Quinidine        | CYP3A4 inhibition; P-glycoprotein inhibition |
| Quinine          | CYP2C8 inhibition; P-glycoprotein inhibition |
| Ranitidine       | CYP3A4 inhibition                 |
| Ritonavir        | P-glycoprotein inhibition         |

Note: This is not a complete list of all loperamide medication interactions; other medications may interact with loperamide through similar mechanisms. CYP, cytochrome P450.

loperamide-specific testing may not be available at all institutions. Additionally, large doses may lead to higher levels and a significantly prolonged half-life.

This case is unique because it was complicated by recurring polymorphic VT and refractory cardiogenic shock. Mechanical support was considered warranted because the patient’s shock could not be successfully managed with inotropes. This strategy highlighted a lack of awareness of recognizing and managing loperamide intoxication, and the patient experienced multiple complications, including arteriotomy site bleeding and HITT. An alternative strategy could have been overdrive pacing with a transvenous pacemaker to suppress polymorphic VT. This may have allowed up-titration of vasoactive agents to manage hypotension while minimizing recurrent arrhythmias.

As awareness of opioid abuse has steadily increased in recent years, relatively little awareness exists regarding loperamide’s fatal arrhythmogenic potential. Reported cases of loperamide-associated mortality have increased sharply between 2014 and 2016, concurrent with the promotion of loperamide’s euphoric effects and symptom-withdrawal management by online forums.

In January 2016, the FDA released a safety announcement outlining loperamide’s proarrhythmic effects, including cardiac arrest and death, and stated that loperamide should be considered as a possible cause of unexplained cardiac events. In January 2018, the FDA subsequently announced plans to reduce over-the-counter loperamide package size to minimize abuse potential.

However, both loperamide and cimetidine, a common booster, are available over the counter without restriction. Given the ongoing opioid crisis, further efforts to minimize abuse potential should be considered. Clinicians should monitor for potential drug–drug interactions in all patients taking loperamide and should screen for electrocardiographic abnormalities in patients taking chronic and/or high-dose loperamide. Because of relatively low bioavailability in patients receiving standard doses without concomitant interacting medications, loperamide may be used cautiously in patients with pre-existing QTc abnormalities if clinically necessary.

Lead author biography

Jonathan D. Cicci graduated from the Ernest Mario School of Pharmacy at Rutgers University in 2011. He completed his PGY1 pharmacy practice residency and PGY2 cardiology specialty residency at the University of North Carolina Medical Center in 2012 and 2013. Since 2013, he has worked at the University of North Carolina Medical Center as a cardiology clinical specialist on the Cardiac Intensive Care Unit and General Cardiology services and as an Assistant Professor at the University of North Carolina Eshelman School of Pharmacy.

Supplementary material

Supplementary material is available at European Heart Journal - Case Reports online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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