

Unexpected Serious Cardiac Arrhythmias in the Setting of Loperamide Abuse

SOMWAIL RASLA, MD; AMY ST. AMAND, PharmDC; MARINA K. GARAS, DO; AMR EL MELIGY, MD; TARO MINAMI, MD, FACP, FCCP

ABSTRACT

Loperamide (Imodium) is a non-prescription opioid receptor agonist available over-the-counter for the treatment of diarrhea. When ingested in excessive doses, loperamide can penetrate the blood-brain barrier and is reported to produce euphoria, central nervous system and respiratory depression, and cardiotoxicity. There is an emerging trend in its use among drug abusers for its euphoric effects or for self-treatment of opioid withdrawal. We report a case of ventricular dysrhythmias associated with loperamide abuse in a 28-year-old man who substituted loperamide for the opioids that he used to abuse.

KEYWORDS: Ventricular tachycardia, Loperamide, opioid abuse, QTc prolongation, Arrhythmias

INTRODUCTION

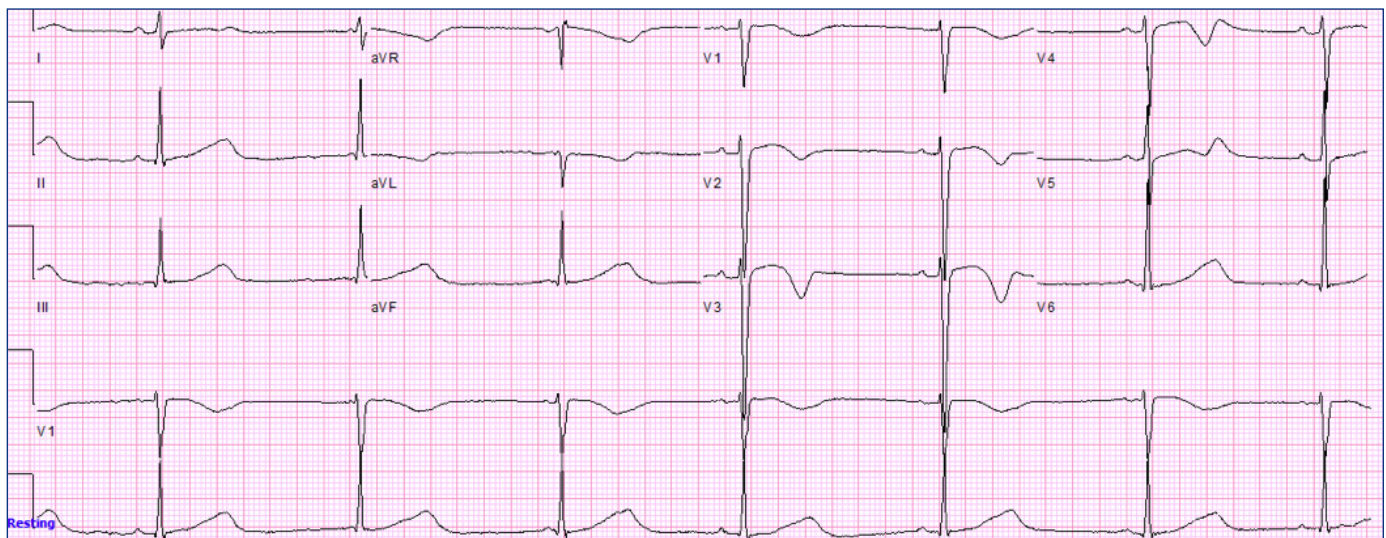
Opioid abuse is one of the main causes of morbidity and mortality in the United States. Loperamide is an over-the-counter opioid receptor agonist used for the treatment of diarrhea. Loperamide abuse is a growing concern that requires careful medical attention. There is an increasing use of loperamide for its euphoric effects or for self-treatment

of opioid withdrawal. We report a case of ventricular tachycardia in the setting of loperamide abuse.

CASE REPORT

A 28-year-old man with post-traumatic stress disorder and remote history of opioid abuse was admitted to the inpatient psychiatric unit for loperamide abuse. The patient is a veteran and bodybuilder who had been abusing loperamide for five months. He was taking about 400 mg daily (recommended dose: 4 mg plus 2 mg after each loose stool, with maximum dose of 16 mg/d) after he ran out of Oxycodone (100-150 tabs daily). Prior to the admission, he experienced three episodes of rapid heartbeats followed by near syncope. The patient denied any family history of sudden death or dysrhythmias. On the second hospital day, while moving from a recumbent position, he felt a skipped heartbeat, followed by palpitations and faintness. On examination, he was noted to have regular rhythm and a 3/6 systolic ejection murmur at the left parasternal border, non-radiating with otherwise normal exam including orthostatic vital signs. An electrocardiogram revealed sinus rhythm at the rate of 50 beats per minute with a prolonged QTc at 601 milliseconds and T-wave inversions precordially (**Figure 1**). The patient's electrolytes were within normal limits and troponin was negative. All

Figure 1. Sinus bradycardia at 50 BPM, premature atrial complexes, T-wave inversion in V2, V3, V4 and aVL leads, and prolonged QTc at 601 ms, PR 200 ms.



his other medications including Fluoxetine, Prazosin, and Quetiapine were discontinued. Pacer pads were applied and the patient was transferred to the ICU for close monitoring. While in the ICU, he developed sinus bradycardia with a persistent prolonged QTc despite an infusion of six grams of magnesium sulfate. A continuous isoproterenol infusion was begun. A transthoracic echocardiogram revealed a normal ejection fraction of 60% with mild apical hypertrophy. Overnight he had a brief episode of nonsustained ventricular tachycardia (VT) (Figure 2). The patient's QTc remained prolonged at 600 milliseconds on the third hospital day. Due to

dynamic EKG changes including intermittent T-wave inversions, he was evaluated with coronary angiography, which did not reveal any evidence of obstructive coronary artery disease or congenital coronary anomalies. Due to the apical hypertrophy, cardiac magnetic resonance imaging (cMRI) was performed to rule out infiltrative cardiomyopathy and the results were negative with no evidence of underlying anatomical cardiac pathology. The QTc interval improved to 459 milliseconds on the fifth hospital day (Figure 3). An exercise stress test prior to discharge showed no significant change in the QTc interval, which ruled out congenital long

Figure 2. Telemetry rhythm strip showing a run of non-sustained Ventricular tachycardia.

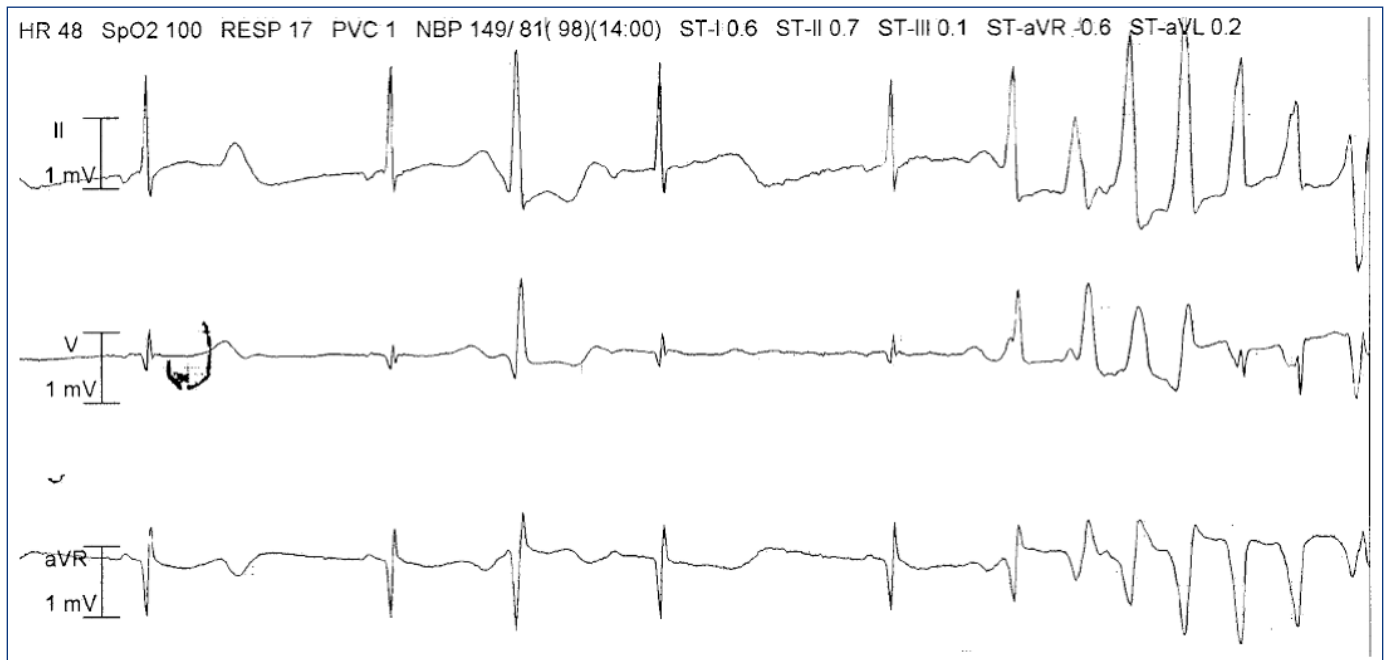
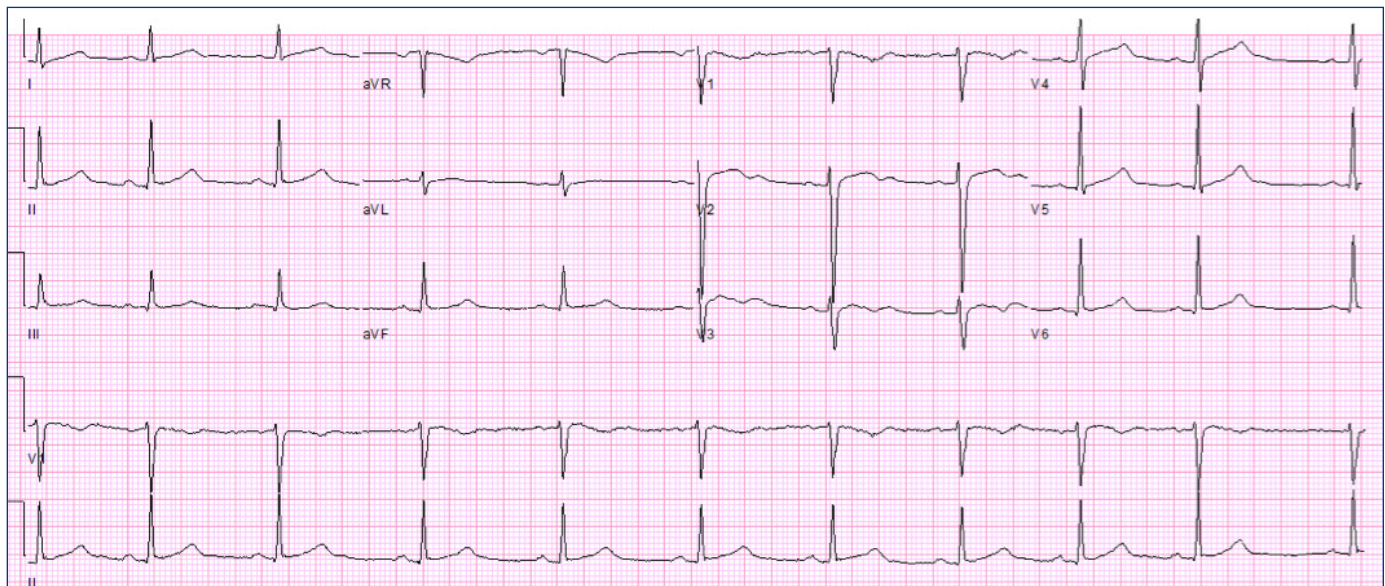


Figure 3. Normal Sinus Rhythm at 66 BPM, QTc interval 459ms, PR interval 170 ms, QRS 88 ms.



QT syndrome. He did not have any recurrent episodes of tachyarrhythmia, including polymorphic ventricular tachycardia and he was discharged on the ninth hospital day with a cardiac event monitor for 14 days. This did not reveal any signs of underlying ventricular arrhythmias except for occasional asymptomatic bradycardia.

DISCUSSION

In the United States, the prescription opioid abuse epidemic is a major public health concern. Efforts such as the prescription monitoring program, physician and patient education, tamper-resistant prescription pads, referral to pain specialists, use of abuse-deterrent formulations of opioids, and requiring patients to present photo identification to pick up opioid prescriptions at the pharmacy are currently being utilized to limit the abuse, misuse, and diversion of prescription opioids. Such restrictions may result in individuals pursuing alternative options, including intentional misuse of loperamide as a readily accessible and inexpensive opioid substitute.^[1]

Loperamide is a non-prescription opioid receptor agonist available over the counter for the treatment of diarrhea. At the recommended doses, loperamide works on the peripheral mu-opioid receptor in the myenteric plexus to slow down peristaltic movements. At low doses, loperamide has little to no effect centrally due to poor oral bioavailability, extensive first-pass hepatic metabolism, and nominal blood-brain barrier penetration due to p-glycoprotein efflux.^[2, 3] Therefore, concomitant use of medications that inhibit hepatic metabolism via cytochrome P450 (CYP) 3A4 (e.g. ketoconazole, itraconazole, clarithromycin, erythromycin, cimetidine, ranitidine and ritonavir) and CYP2C8 (e.g. gemfibrozil) or increase blood-brain barrier penetration via inhibition of p-glycoprotein (e.g. quinidine) may increase loperamide serum concentrations and intensify the risk of toxic effects.

When ingested in excessive doses, loperamide can penetrate the blood-brain barrier and is reported to produce euphoria, central nervous system and respiratory depression, and cardiotoxicity.^[2] Therapeutic doses result in a serum loperamide concentration between 0.24 and 1.2 ng/mL. At typical doses of loperamide (2-8 mg), the half-life of loperamide is 9-13 hours, but the half-life may increase following ingestion of larger doses due to slowed gastrointestinal motility and longer exposure time, leading to prolonged toxicities, as seen in our case.^[4] Serum loperamide levels must be obtained in the setting of suspected abuse because standard drug screens for opioids do not include an assay for loperamide and will yield negative results.^[5]

At supra-therapeutic concentrations, loperamide can cause electrocardiographic abnormalities, including prolongation of the QTc interval. Case reports of loperamide abuse describe instances of cardiac conduction disturbances including ventricular tachycardia or fibrillation,

torsades de pointes, cardiac arrest and sudden cardiac death. In some case reports, dysrhythmia attributable to loperamide has been refractory to lidocaine, magnesium sulfate, amiodarone, sodium bicarbonate, potassium chloride, fatty acid emulsion, and repeated cardioversion/defibrillation. Loperamide-induced dysrhythmias refractory to standard medical therapy may be responsive to electrical overdrive pacing or to isoproterenol continuous infusion, which is corroborated by our case report.^[1]

As a piperidine derivative, the mechanism of loperamide-induced cardiotoxicity is theorized to be due to dose-dependent effects on the voltage-gated L-type calcium channels, hERG/I_{Kr} potassium channel and cardiac sodium channels, similar to the action of Vaughan-Williams class IA, III, and IV anti-arrhythmics. Class IA agents such as quinidine, procainamide, and disopyramide lengthen refractory period, widen the monophasic action potential, and slow conduction via cardiac sodium channel blockade. The most serious side effect of cardiac sodium channel blockade include QRS prolongation, polymorphic ventricular tachycardia and torsades de pointes. Class III agents such as sotalol, ibutilide, and dofetilide block the cardiac potassium channel, delaying repolarization, which can cause QT prolongation. Class IV agents such as diltiazem and verapamil block cardiac calcium channels in the sinoatrial and atrial-ventricular nodes, reducing heart rate and conduction, which can result in bradyarrhythmia. Loperamide is known to exhibit its anti-secretory effects in the gastrointestinal tract through inhibition of calcium channels.^[1, 4]

Loperamide abuse for euphoric, opioid-like effects or self-treatment of opioid withdrawal symptoms is an emerging trend. In June 2016, the Food and Drug Administration (FDA) issued a warning statement to health care providers about potential serious adverse outcomes, including cardiac dysrhythmias and mortality.^[6] Data from the National Poison Data System indicate a national increase in intentional loperamide misuse. The risk factors for loperamide abuse include young age, male gender, previous opioid dependence or abuse, and previous treatment with methadone or buprenorphine. According to epidemiologic analysis, co-ingestions include antidepressants, analgesics, and benzodiazepines.^[5]

CONCLUSION

Our case highlights the importance of educating both the public and health care providers of the potential life-threatening effects of loperamide abuse in the context of the opioid addiction epidemic in the United States. Loperamide is inexpensive and readily accessible in pharmacies without a prescription or governmental regulation. Loperamide-induced cardiac dysrhythmias should be on the differential diagnosis in patients with a history of opioid abuse or dependence who present with cardiac arrest or syncope with abnormal electrocardiographic findings. Clinicians should report such cases to FDA Medwatch.^[5]

References

1. Marraffa J, Holland M, Sullivan R, Morgan B, Oakes J, Wiegand T, et al. Cardiac conduction disturbance after loperamide abuse. *Clinical Toxicology*. 2014;52:952-7.
2. Eggleston W. Notes from the Field: Cardiac Dysrhythmias After Loperamide Abuse—New York, 2008–2016. *MMWR Morbidity and Mortality Weekly Report*. 2016;65.
3. Enakpene EO, Riaz IB, Shirazi FM, Raz Y, Indik JH. The long QT teaser: loperamide abuse. *The American journal of medicine*. 2015;128:1083-6.
4. Eggleston W, Nacca N, Marraffa JM. Loperamide toxicokinetics: serum concentrations in the overdose setting. *Clinical Toxicology*. 2015;53:495-6.
5. Vakkalanka JP, Charlton NP, Holstege CP. Epidemiologic Trends in Loperamide Abuse and Misuse. *Ann Emerg Med*. 2017;69:73-8.
6. Persson PB. Opiate of the masses. *Acta Physiologica*. 2016;217:270-1.

Authors

Somwail Rasla, MD, Department of Medicine, Memorial Hospital of Rhode Island, Pawtucket, RI; The Warren Alpert Medical School of Brown University.

Amy St. Amand, PharmDc, Department of Medicine, Memorial Hospital of Rhode Island, Pawtucket, RI; College of Pharmacy, University of Rhode Island.

Marina K. Garas, DO, Department of Anesthesia and Perioperative Medicine, Tufts Medical Center, Boston, MA; Tufts University School of Medicine.

Amr El Meligy, MD, Department of Medicine, Memorial Hospital of Rhode Island, Pawtucket, RI; The Warren Alpert Medical School of Brown University.

Taro Minami, MD, FACP, FCCP, Division of Pulmonary, Critical Care, and Sleep Medicine, Memorial Hospital of Rhode Island, Pawtucket, RI; The Warren Alpert Medical School of Brown University.

Correspondence

Somwail Rasla, MD
 Memorial Hospital of Rhode Island
 111 Brewster St. Pawtucket, RI 02860
 401-729-2221
somwail_rasla@brown.edu