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CLINICAL DECISION MAKING

Torsade de Pointes Associated with High-dose Loperamide Ingestion

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ABSTRACT. Loperamide, a peripherally-acting µ-opioid receptor agonist available over-the-counter for treatment of diarrhea, is not known to prolong the QTc interval. The oral bioavailability of loperamide is poor due to intestinal p-glycoprotein activity and considerable first-pass metabolism by cytochrome P450 (CYP) CYP3A4. Cimetidine is a potent inhibitor of p-glycoprotein and CYP3A4. Coincident ingestion of loperamide and cimetidine may result in significantly elevated serum loperamide levels. We report a case of a 26 year-old man with prior opioid abuse who presented to our hospital with recurrent torsade de pointes after ingestion of cimetidine and large doses of loperamide. Electrocardiogram in sinus rhythm revealed a markedly prolonged QTc interval. Isoproterenol infusion was begun, and no further episodes of torsade de pointes occurred. Following two weeks of observation, the QTc interval normalized. Our patient reported taking cimetidine along with large doses of loperamide to simulate the euphoric effects associated with prior prescription opioid abuse. He learned about this effect from a website designed for sharing information amongst drug abusers. This case raises concern for a growing public health danger that warrants increased vigilance among clinicians as loperamide is inexpensive, widely available without a prescription, and presently is not characterized as a QTc prolonging drug.

KEYWORDS. drug abuse, loperamide, QTc prolongation, torsade de pointes.

Introduction
Opioids are generally considered devoid of cardiac electrophysiological properties. However, methadone, a central-acting µ-opioid receptor agonist that is structurally similar to loperamide, has been associated with dose-dependent QTc interval prolongation and torsade de pointes (TdP).1 Loperamide is an over-the-counter peripherally acting µ-opioid receptor agonist that is increasingly being used as a drug of abuse. In this report, we describe a case of TdP associated with ingestion of high-dose loperamide and cimetidine in a patient with prior prescription opioid abuse.

Case report
A 26-year-old man with prior opioid abuse presented to our hospital with recurrent syncope after ingesting high doses of loperamide for several months. On arrival, he developed TdP requiring electrical cardioversion. An electrocardiogram (ECG) obtained in sinus rhythm revealed a markedly prolonged QTc interval of >700 ms (Figure 1). Given a heart rate of 85 bpm and a markedly prolonged QTc interval, isoproterenol infusion was initiated to prevent bradycardia-induced arrhythmia recurrence. No further episodes of TdP occurred during hospitalization. Serum magnesium, potassium, and calcium levels were all within normal limits, and no other drugs associated with QTc prolongation were detected on urine toxicology. Transthoracic echocardiogram revealed mildly reduced systolic function with preserved basal wall motion and apical dyskinesis consistent with stress-induced cardiomyopathy. Coronary angiography did not demonstrate obstructive atherosclerosis.

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The history was notable for severe constipation and no bowel movement during the 7 days prior to presentation. Our patient reported ingesting 100–250 mg of loperamide with 400 mg of cimetidine daily to simulate the euphoric sensation associated with his prior prescription opioid abuse. He learned about the use of high-dose loperamide and the ability of cimetidine to augment its opioid-agonist effects on a website designed for sharing information amongst drug abusers. After prolonged hospitalization, QTc interval and left ventricular systolic function normalized and regional wall motion abnormalities resolved. An ECG obtained 2 months post hospitalization revealed a normal QTc of 420 msec (Figure 2).

**Discussion**

There are two reported cases of QTc interval prolongation and TdP potentially related but not attributed to loperamide ingestion. The first involved a 28-year-old man who ingested amitriptyline and 100 mg of loperamide. Notably, TdP was attributed to amitriptyline despite a normal serum amitriptyline level. Similarly, the second case involved a 28-year-old man with Crohn’s disease who ingested 120 mg of loperamide daily as an antidiarrheal and developed unremitting ventricular tachycardia. Loperamide is not currently categorized as a QTc-prolonging drug in a dynamic public registry (http://www.crediblemeds.org/everyone/composite-list-allqtdrugs).

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**Figure 1:** Electrocardiogram at time of presentation demonstrating marked QTc interval prolongation.

**Figure 2:** Electrocardiogram at 2 months post hospitalization with normal QTc interval duration.
However, methadone, another synthetic opioid, has been associated with QTc prolongation and TdP. Unlike methadone, loperamide is a peripherally acting μ-opioid receptor agonist with poor oral bioavailability due to limited gut absorption and considerable first-pass metabolism. The low bioavailability may in part be explained by the activity of intestinal p-glycoprotein, which limits transmural uptake of the drug. Loperamide is biotransformed into its main *in vivo* metabolite, N-desmethyloperamide, by cytochromes P450 (CYP) CYP3A4 and CYP2C8. Inhibition of p-glycoprotein, CYP3A4, and CYP2C8 increases serum levels of loperamide significantly. Increased serum loperamide levels result in respiratory depression, suggesting a centrally acting opioid effect may be achieved at elevated serum concentrations.

The mechanism of QTc prolongation due to loperamide is unknown. However, QTc prolongation related to other synthetic opioids has been recognized to be due to blockade of the cardiac human ether-a-go-go (hERG) potassium channel. It is possible that loperamide blocks hERG, though this has not been completely investigated. Our patient simultaneously ingested cimetidine along with very large doses of loperamide. Cimetidine may have increased serum levels of loperamide through inhibition of both p-glycoprotein and CYP3A4. The blockade of hERG by other synthetic opioids and increased serum levels of loperamide associated with coincident ingestion of cimetidine suggest a biologically plausible mechanism.

Loperamide shares structural features with methadone as well as the potent hERG blocker terfenadine. All three molecules have multiple phenyl rings, and terfenadine and loperamide share a piperidine nitrogen thought to facilitate block within the hERG channel pore. Additional indirect evidence includes the finding that loperamide potently inhibits the hERG channel using a thallium flux assay. However, confirmatory electrophysiologic data have not been published to our knowledge. While a causal relationship between loperamide and TdP has not been previously established, a validated adverse drug reaction probability scale suggests that the association is probable (score of 6 out of a possible 13). Our patient ingested large doses of loperamide along with cimetidine in an attempt to simulate the euphoric effects of prior prescription opioid abuse. He learned about this effect on a website designed for sharing information among drug abusers. Ingestion of high-dose loperamide for self-treatment of opioid withdrawal and as a drug of abuse appears to be increasing through internet dissemination. The increasing use of large doses of loperamide coincident with other drugs that increase serum loperamide levels and the associated potential risk of QTc prolongation and TdP may represent a growing public health danger.

**Conclusion**

We report a case of markedly prolonged QTc and recurrent TdP in a patient who ingested large doses of loperamide coincident with cimetidine in an attempt to simulate the euphoric effects associated with opioid abuse. This is a sentinel case, as ingestion of large doses of loperamide for self-treatment of opioid withdrawal and as a drug of abuse appears to be increasing through internet dissemination. This may represent a growing public health danger and warrants further investigation. Greater health-care professional awareness of loperamide abuse and further study of its effects on the hERG cardiac potassium ion channel are warranted. In the interim, the Food and Drug Administration should reconsider the over-the-counter availability of loperamide.

**References**


