Surreptitious Loperamide Abuse Induced Torsade de Pointes

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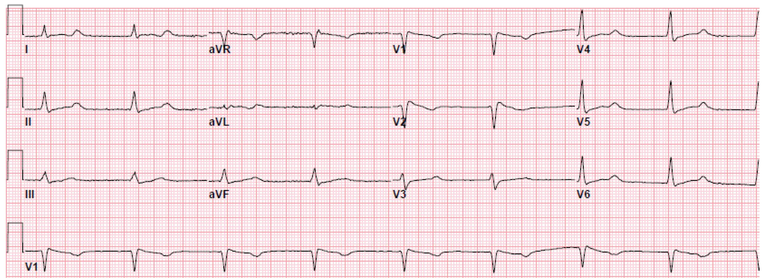
INTRODUCTION

Loperamide is well-known as a widely-available, inexpensive over-the-counter (OTC) antidiarrheal medication. It is less well-known as a potent μ-opioid receptor agonist with euphoric or analgesic effects at high doses. Loperamide misuse and abuse have rapidly increased in the past decade, in the midst of new opioid laws and regulations. As a result, the cardiotoxic effects of the drug have come to light, but remain under recognized clincally

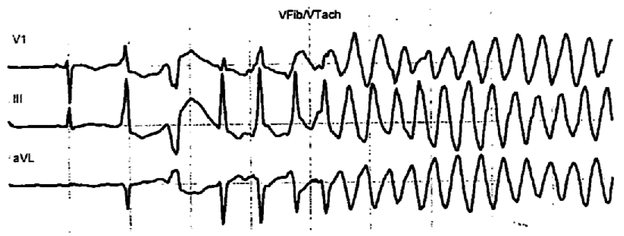
CASE PRESENTATION

A 28-year-old female with a history of nephrolithiasis was admitted for acute pyelonephritis. She denied a family history of sudden cardiac death or arrhythmias and initially denied use of any medications or illicit drugs. ECG on admission showed junctional rhythm with a ventricular rate of 50 bpm and QTc of 550 ms. QT prolonging medications, including anti-emetics and fluoroquinolones were avoided. Labs were pertinent for potassium of 3.9 mmol/L and magnesium of 1.5 mg/dL, which were adequately repleted. On hospital day 3, she had one episode of nonsustained TdP which self-terminated before she was given IV magnesium. Isoproterenol infusion was initiated and continued for 2 days to maintain sinus rhythm with rates in the 90s due to concern for pause-dependent TdP in the setting of bradycardia. Shortly after isoproterenol was weaned off, patient again developed frequent nonsustained TdP with one episode degenerating into sustained monomorphic ventricular tachycardia requiring synchronized cardioversion. Patient subsequently admitted to taking up to 360 mg of loperamide daily (I capsule is 2 mg in stregnth) and family members confessed to bringing her the medication while she was hospitalized. Taking the half-life of loperamide into consideration, isoproterenol was restarted and continued for 10 days. Additionally, patient required treatment for opioid withdrawal. Upon discharge to substance rehab, ECG showed narrow QRS complexes with QTc ranging from 460 to 480 ms.

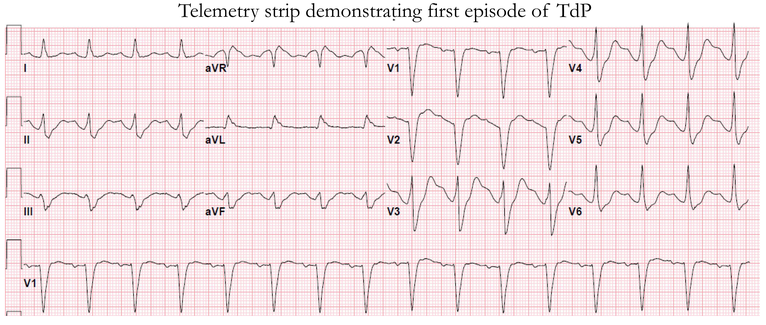
IMAGES



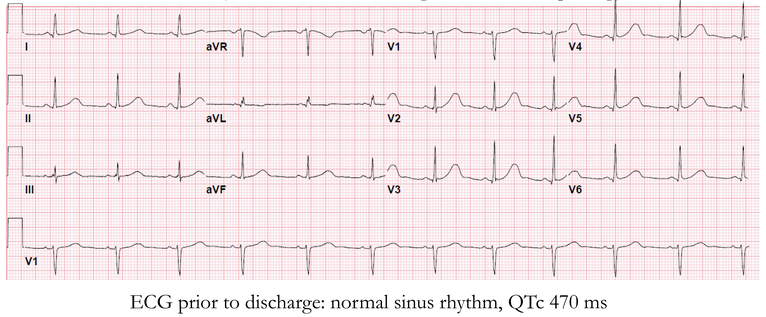
Admission ECG: junctional rhythm, QTc 550 ms



Telemetry strip demonstrating first episode of TdP



ECG on hospital day 5 after weaning off isoproterenol and just prior to recurrent TdP: sinus rhythm with QRS widening in a LBBB morphology



ECG prior to discharge: normal sinus rhythm, QTc 470 ms

DISCUSSION

Loperamide was previously considered to have low abuse potential due to its extensive first-pass metabolism mediated by cytochrome P450 inhibition and its poor blood-brain barrier penetration due to P-glycoprotein efflux transporters. However, significantly higher dosages in combination with cytochrome P450 or P-glycoprotein inhibitors (including grapefruit juice and tonic water) can facilitate central nervous system effects and cause bradycardia, ventricular tachycardias, and cardiac arrest. Previous case reports have shown cardiotoxicity at doses ranging from 134 to 400 mg daily, well over the recommended daily maximum dose of 16 mg. The proposed mechanisms of its proarrhythmogenic effects are 1) antagonism of the hERG potassium channel $K_v11.1$ responsible for I_{Kr} resulting in QTc prolongation and increasing the risk for TdP, 2) inhibition of the sodium channel $Na_v1.5$ resulting in QRS widening. Both QTc prolongation leading to TdP and QRS widening were seen in our patient.

Management of loperamide induced ventricular tachycardia remains supportive. Serum loperamide levels should be checked and trended if available. Activated charcoal is not helpful in chronic use and hemodialysis is likely ineffective due to high protein binding. IV magnesium is considered standard treatment in TdP but chronotropic agents and transvenous or transcutaneous pacing may be required in large dose ingestions. There is little data on the use of antiarrhythmic agents.

CONCLUSION

The abuse potential and cardiotoxic effects of loperamide remain underrecognized. Thorough medication reconciliation (both prescription and OTC) and increased provider awareness of loperamide's side effects are crucial first steps in the prevention of fatal arrhythmias and cardiac death.

References:
Teigeler, Todd et al. "Electrocardiographic changes in loperamide toxicity: Case report and review of literature." *Journal of cardiovascular electrophysiology* vol. 30,11 (2019): 2618-2626. doi:10.1111/jce.14129
Cicci, Jonathan D et al. "Loperamide overdose causing torsades de pointes and requiring Impella temporary mechanical support: a case report." *European heart journal. Case reports* vol. 3,4 (2019): 1-6. doi:10.1093/ehjcr/ytz150