

Conduction Disturbances and Ventricular Arrhythmias Associated with High-Dose Loperamide

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Abstract

Although loperamide has been widely used for the treatment of diarrhea, there is growing popularity over its abuse potential in alleviating opioid-withdrawal symptoms and achieving euphoria. Toxic levels of loperamide have been associated with life-threatening ventricular tachyarrhythmias and cardiac arrest. We report a case of high-dose loperamide ingestion in a patient presenting initially with unstable bradycardia followed by episodes of polymorphic ventricular tachycardia, and an unmasked Brugada ECG pattern. This is the first such report of the Brugada pattern being unmasked on ECG with loperamide ingestion. The patient stabilized with supportive care without the need for inotropic support. We discuss potential mechanisms of toxicity leading to conduction abnormalities and provide a literature review of all published cases of loperamide toxicity to describe proposed treatment options. Recognition of the abuse potential and hazards of this over-the-counter anti-diarrheal therapy will alert the clinician of associated toxidromes and management strategies.

Keywords: Loperamide; Arrhythmia; QT prolongation; QRS prolongation; Brugada pattern; Torsades de pointes

Introduction

Loperamide is an over-the-counter, peripherally-acting, μ -opioid receptor agonist used for the treatment of diarrhea [1]. It undergoes considerable first-pass metabolism, and intestinal absorption is incomplete with poor central nervous system (CNS) penetration related to P-glycoprotein expression limiting abuse potential. However, web-forum analyses over recent years reveal increased discussion of extra-medical uses of loperamide to alleviate opioid-withdrawal symptoms and to achieve euphoria [2]. Further, a series of recently-published cases reveals an association with recreational loperamide use (and significantly elevated serum concentrations) with electrocardiographic derangements including QRS complex and QT interval prolongation thought to be related to sodium channel blockade, and potassium channel blockade, respectively, as well as monomorphic ventricular tachycardia and torsades de pointes (TdP) [3-5]. We present a case of high-dose loperamide ingestion leading to bradyarrhythmias, prolongation of the QRS complex and QTc interval, unmasking of Type I Brugada pattern, and episodes of TdP.

Case Presentation

A 48 year-old woman, with past medical history significant for alcoholic cirrhosis, depression on sertraline and clonazepam, and polysubstance abuse, was brought into our emergency department by EMS when found appearing somnolent and intoxicated by her daughter. She was noted to be bradycardic with a heart rate of 40-50 beats per minute (BPM) and hypotensive with an initial blood pressure of 70/40 mmHg. Her exam was significant for somnolence without a focal neurological deficit, and a distended abdomen. Laboratory data was significant for serum creatinine of 2.3 mg/dl (0.6 mg/dl baseline),

Potassium of 6.2 mmol/l, Magnesium of 1.5 mg/dl, Calcium of 9.9 mg/dl, and ethanol level of 18.0 mg/dl. Her initial electrocardiogram (ECG) was notable for junctional rhythm, junctional premature complexes, and premature ventricular complexes (PVCs) with QRS duration of 120 ms, and QT/QTc of 560/620 ms (Figure 1). Her baseline ECG one year prior was normal sinus rhythm with normal QRS complex and QT interval.

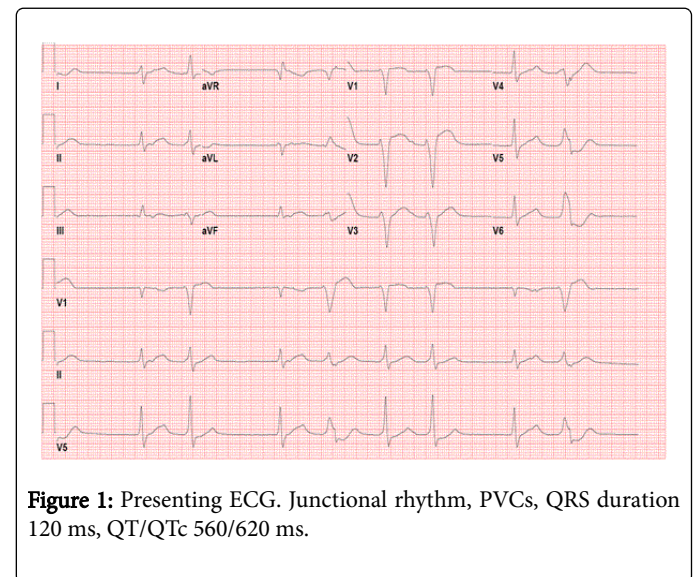


Figure 1: Presenting ECG. Junctional rhythm, PVCs, QRS duration 120 ms, QT/QTc 560/620 ms.

After administration of 2 liters of intravenous normal saline, 45 mEq sodium bicarbonate, 2 g calcium gluconate, insulin, and 2 g magnesium sulfate, her blood pressure and heart rate improved without the need for vasopressor support. Electrolytes normalized, but subsequent ECG revealed sinus bradycardia and competing junctional rhythm, QRS duration of 140 ms, QT/QTc of 600/600 ms, and a Type I

Brugada pattern evident in leads V1-2 (Figure 2). She was admitted to the medical intensive care unit (MICU) for further monitoring and consideration for transvenous pacer insertion for overdrive pacing in case of malignant ventricular tachyarrhythmia. Her transthoracic echocardiogram (TTE) revealed normal bi-ventricular and valvular function. The patient experienced frequent brief runs of polymorphic ventricular tachycardia on overnight monitoring without associated symptoms. After 2 additional boluses of 2 g IV magnesium sulfate and 2 boluses of 45 mEq sodium bicarbonate, events decreased in frequency and fully abated over the next 24 hours. Serial ECGs were significant for ongoing, yet decreasing prolongation of QT and QRS with persistent Brugada pattern. Given the lack of sustained ventricular arrhythmias and decrease in frequency of brief TdP runs, inotrope infusion and overdrive pacing were withheld. Intravenous lipid emulsion, available at bedside, was not deemed necessary given the described improvement.

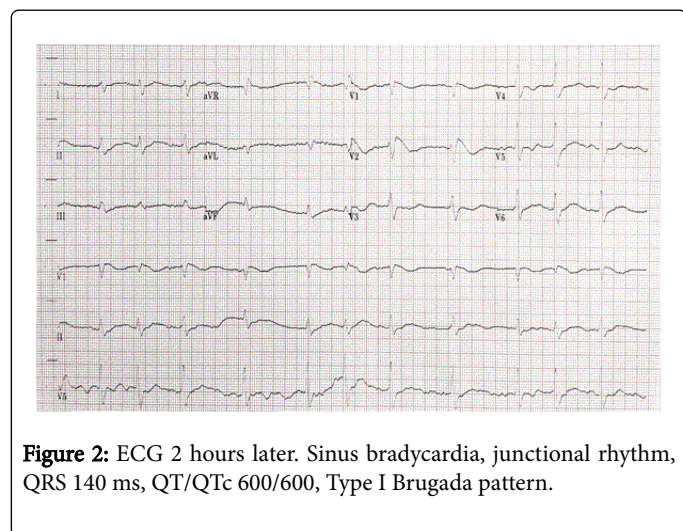


Figure 2: ECG 2 hours later. Sinus bradycardia, junctional rhythm, QRS 140 ms, QT/QTc 600/600, Type I Brugada pattern.

The patient returned to baseline mental status the morning following admission and on further questioning, admitted to taking over 240 mg loperamide over the past few days (maximum daily dose

16 mg) in addition to continued clonazepam and alcohol intake to achieve a high and prevent alcohol and benzodiazepine withdrawal. Toxicology labs the subsequent day reported a loperamide level of 43 ng/ml (reporting limit of 5 ng/ml) while negative for opiates and tricyclic antidepressants. On further questioning, the patient admitted to prior episodes of unheralded syncope over the past years when sober. She was discharged from the MICU after 2 days of monitoring and repeat ECG 3 days later was notable for sinus tachycardia at 114 BPM, QRS duration of 82, QTc of 460, with loss of the Brugada pattern. She was offered an inpatient psychiatric admission and further cardiac evaluation, but left against medical advice prior to additional workup.

Discussion

We present a case of loperamide-induced QRS and QTc prolongation, bradyarrhythmias, Brugada pattern, and episodes of TdP with resolution of electrocardiographic abnormalities after withdrawal of the offending agent. Despite co-administration of a selective serotonin receptor inhibitor, sertraline, the patient denied abuse and had been on it chronically with an ECG three months prior showing normal sinus rhythm without QRS or QTc prolongation, or Brugada pattern. Further, the patient did not exhibit any signs and symptoms of serotonin syndrome, such as agitation, tachycardia, hypertension, vomiting, or tremor. The patient had a structurally normal heart, and literature review confirmed identical presentations associated with loperamide overdose. While other aforementioned electrocardiographic abnormalities have been described in scant case reports [3-5], to our knowledge, this is the first case report of this agent unmasking a Brugada pattern. Previous reports describe markedly elevated serum loperamide concentrations with presentations including life-threatening ventricular tachyarrhythmias, and varying degrees of QRS and QTc prolongation. Those patients were either managed with isoproterenol infusion, overdrive transvenous pacing in cases of sustained ventricular arrhythmias or cardiac arrest, or observed without intervention in the absence of sustained arrhythmia. Table 1 summarizes previous case reports in terms of presentation and management.

Patient	Initial presentation	Loperamide, Other medications	Course, Treatment and Outcome	Reference
28 y/o PMH Crohn's disease, polysubstance abuse, depression.	Collapsed, ventricular tachycardia (successfully cardioverted). ECG: QTc 647 ms, QRS 162 ms Potassium 3 meq/l otherwise normal electrolytes.	20-30 tablets of loperamide (40-60 mg) and 67 tablets day prior to admission Amitriptyline 75-150 mg	Initially diagnosed with TCA overdose (later level came back normal). Treated with sodium bicarbonate, magnesium, lidocaine. Continued to have bradycardias and polymorphic VTs requiring multiple cardioversions and transvenous pacing. Continued to have prolonged QTc (max 883 msec) and QRS (max 196 msec) requiring isoproterenol drip (continued for 5 days with successful return to normal).	Pokhrel et al. [6]
28 y/o PMH polysubstance abuse, depression, small bowel obstruction, and Crohn's disease.	Found pulseless at home with witnessed seizures and ventricular tachycardia, return of spontaneous circulation after ACLS. Multiple ECGs showed interventricular conduction delay and QTc of 850 msec, ventricular fibrillation/tachycardia.	60 tablets of loperamide (120 mg) daily Amitriptyline 150-200 mg daily (elevated level at 130 ng/ml)	Defibrillated multiple times with temporary resolution. Required temporary pacemaker insertion and isoproterenol for TdP and bradycardia with resolution several days later.	Banas et al. [7]

25 y/o recently diagnosed with long QT syndrome (denied any drug use at that time).	Nausea, vomiting bradycardia, shock	Found to have empty bottles of loperamide in her apartment (unknown amount of ingestion), found to have an elevated loperamide level at 32 ng/ml.	Required intubation and multiple vasopressors, multiple episodes of unstable polymorphic ventricular tachycardia. Suspected to have sodium channel blocker toxicity due to widened QRS complexes and started on bicarbonate infusion with mild improvement in QRS duration (toxicology screen came back negative). After empty bottles of loperamide were found, patient was continued on bicarbonate drip and started on lipid emulsion therapy. ECG abnormalities resolved within 1 week.	Enakpene et al. [8]
43 y/o PMH opioid abuse not on chronic medications.	Several episodes of TdP. ECG: normal sinus with QRS of 130 ms and QTc of 684 msec with frequent PVCs.	144 tablets of loperamide daily to manage opioid withdrawal	TdP refractory to lidocaine, amiodarone, sodium bicarbonate, magnesium, and fatty acid emulsion and repeated cardioversion (15 shocks). Finally controlled with with transvenous pacemaker continued until resolution at day 3.	Marraffa et al. [3]
33 y/o no reported PMH or chronic medications.	Shortness of breath with stable vitals ECG: QRS 128 msec, QT/QTc 566/636 msec	60-100 tablets of loperamide over 6 hours as opioid substitute (loperamide level of 77 ng/ml).	Sodium bicarbonate (3 ampules), magnesium sulfate, and 40 mEq of intravenous potassium were administered with no change in QRS. Remained stable, with improvement at 24 hours to QRS duration of 100 ms and QTc of 409 msec when patient left against medical leave.	Marraffa et al. [3]
33 y/o PMH opioid and ethanol abuse.	Anxiety, panic, and chest tightness, with hemodynamic stability. ECG: sinus rhythm with QRS 118 msec and QTc of 490 msec and potassium was 3.2 mEq/l.	35 tablets of loperamide daily (2 mg) chronically and on the day of admission took 140 mg of loperamide (level elevated at 33 ng/ml)	Received potassium repletion and magnesium intravenously in addition to benzodiazepines given concern of alcohol withdrawal. No arrhythmias were observed, and QRS improved to 92 msec and QTc to 450 msec.	Marraffa et al. [3]
26 y/o PMH opioid abuse.	Recurrent syncope, TdP requiring cardioversion, QTc > 700 ms	100-150 mg loperamide with 400 mg cimetidine daily for 7 days	Started on isoproterenol infusion initially. Long hospitalization with QTc of 420 on ECG 2 months post initial presentation.	Marzec et al. [4]
54 y/o with diabetes on metformin.	Episodes of syncope ECG: sinus arrest, slow junctional escape rhythm, and PVCs. Normal labs and echocardiogram.	Chronic self-treatment of diarrhea with loperamide taking 144 mg daily for 2 years	Multiple episodes of sustained ventricular tachycardia and hypotension requiring resuscitation, intubation, amiodarone, and lidocaine. A pacemaker was inserted which resulted in suppression of ectopy and ventricular tachycardia. ECG after pacing showed QT interval of 500 msec.	Spinner et al. [5]

Table 1: Previous Case Reports of Loperamide Toxicity.

The QT interval prolongation related to loperamide has been attributed to inhibition of the human ether-a-go-go-related gene (hERG) responsible for the rapid delayed rectifier potassium current (I_{Kr}); a known mechanism of many QT interval prolonging drugs as well as congenital long QT syndrome type 2 (LQTS2) [3,9-11]. This current mediates cardiac myocyte repolarization and terminates the action potential; hERG inhibition leads to delayed repolarization, predisposes to early after-depolarizations (EADs), heterogeneous myocardial repolarization, and TdP [10]. Drug-mediated slowing of cardiac depolarization (QRS complex prolongation) has also been associated with ventricular arrhythmias particularly with the use of Class IC antiarrhythmic drugs in patients with infarcted or ischemic myocardium [11]. Further, Class IC antiarrhythmic agents are known

to cause bradyarrhythmias such as junctional or ventricular escape. Our case, as well as previous reports, demonstrated such effects on both myocardial repolarization as well as depolarization.

The type I Brugada pattern, defined as ≥ 2 mm ST elevation in the right precordial leads with coved appearance and a negative T-wave, is associated with ventricular arrhythmias and sudden cardiac death [12]. Patients may have a normal baseline ECG with induction of the abnormality with drugs or medications with sodium channel blocking properties. The unmasking of the Brugada pattern (often provoked with agents such as cocaine, propofol, tricyclic antidepressants, anesthetics, antiarrhythmic medications, as well as fever or electrolyte imbalance) has been highly-associated with risk for malignant arrhythmias and cardiac arrest [13]. The appearance of a Brugada

pattern has been reported in the context of opiate use, such as methadone ingestion and tramadol overdose in previously-published cases [14,15]. The observation of QRS prolongation and Brugada pattern with high serum loperamide concentration suggests potential of sodium channel blockade in a manner similar to Class I antiarrhythmic medications. This finding leads to an opportunity to identify a patient, and potentially relatives, at elevated risk for sudden cardiac death; unfortunately, the patient left against medical advice prior to the initiation of the workup.

The management of high-dose loperamide ingestion is extrapolated from toxidromes related to sodium channel blocker ingestion as well as management of arrhythmias related to QTc prolonging medications. Our approach was based on ECG findings of prolongation of both intervals in consultation with poison control. Hypertonic sodium salts are the treatment of choice in management of sodium channel blocker overdose (e.g. sodium bicarbonate, sodium lactate) and are often administered when the QRS complex is ≥ 120 ms with bolus dosing in the 50-100 mEq range pending normalization of QRS duration or significant alkalemia [16]. The acute management of acquired long QT syndrome and associated TdP involves correction of underlying electrolyte abnormalities, IV magnesium sulfate bolus (2 g) irrespective of the magnesium level, temporary transvenous cardiac pacing at a rate of 90-110 BPM, or Isoproterenol infusion aimed to maintain a heart rate of >90 BPM [16,17]. The latter strategies are often employed with recurrent TdP not responsive to Magnesium administration as a means to prevent pauses, shorten the QTc interval, and enhance repolarization.

Intravenous intralipid, an emulsion in water of soybean oil, glycerin, and egg phospholipid, is considered a reasonable option in the treatment of serious instability related to highly-lipophilic substance ingestion; an option we considered if the patient were to demonstrate worsening cardiotoxic effects. One proposed mechanism is the formation of a "lipid sink", an intravascular phase that acts to absorb lipophilic free toxin available for myocardial binding. It has been shown to reduce the aqueous plasma concentration of bupivacaine to a much greater extent than expected by hemodilution alone [17,18]. Additional proposed mechanisms of action include the increase of calcium channel current leading to enhanced cardiac function, as well as acting as a direct myocardial energy source [18-20]. Intralipid has been reported effective in cases of local anesthetic, psychotropic drug, beta-blocker, and calcium channel blocker overdoses [18-20]. As our patient had very brief episodes of TdP with improving intervals after sodium bicarbonate and magnesium administration, this therapy was not pursued.

Conclusion

We presented a case describing electrocardiographic conduction abnormalities, TdP, and an unmasked Brugada pattern in the setting of high-dose loperamide ingestion with resolution of aforementioned disturbances by withdrawal of the offending agent, correction of electrolyte abnormalities, and administration of sodium bicarbonate and magnesium sulfate. This case adds to the fairly scant, but growing body of literature describing life-threatening ventricular tachyarrhythmia associated with high-dose loperamide ingestion. Further, this is the first described case of Brugada pattern unmasked in this context. The report adds to the growing awareness of the abuse potential of this over-the-counter medication, and alerts the clinician to recognize associated conduction disturbances and their potential to cause life-threatening arrhythmias.

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