Ventricular Tachycardia Followed by Cardiac Arrest Associated with Chronic Loperamide Abuse

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Abstract

Loperamide is a mu-opioid receptor agonist that works peripherally in the gastrointestinal tract to treat diarrhea. Misuse of this medication results from attempts to achieve opioid-like euphoria or to mitigate opioid withdrawal symptoms by ingesting large doses. Case reports have described the development of QTc interval prolongation and Torsades de Pointes after chronic loperamide use.

Presented below is a case report about a 29-year-old patient who presented with syncope and QTc prolongation due to chronic loperamide overuse. She experienced polymorphic ventricular tachycardia followed by cardiac arrest requiring resuscitation and defibrillation.

Treatment options include insertion of a transvenous pacemaker or pharmacological pacing with isoproterenol. The patient below had a previously implanted pacemaker that was interrogated and adjusted by the electrophysiology team during her stay.

This case report adds to the growing literature supporting the increased need for healthcare professionals to consider chronic abuse of over the counter medications as a differential diagnosis. Loperamide is of increased interest given the severity of the consequences of QTc prolongation and ventricular tachycardia.

Keywords: Loperamide; Ventricular tachycardia; Opioid; QTc prolongation; Cardiac arrest

Abbreviations

USFDA: U.S. Food and Drug Administration; ED: Emergency Department; EP: Electrophysiology; RBBB: Right bundle branch block; ECG: electrocardiogram; AV: atrioventricular; LPFB: Left posterior fascicular block; VT: Ventricular tachycardia; ADR: Adverse drug reaction; OTC: Over the counter; ILE: Intravenous lipid emulsion

Introduction

There are an increasing number of published reports regarding the misuse of loperamide to achieve opioid-like euphoria or to mitigate opioid withdrawal symptoms [1-6]. Loperamide, readily available as an over-the-counter antidiarrheal medication, is a μ-opioid receptor agonist and is structurally similar to opioids. At U.S. Food and Drug Administration (FDA) approved doses, loperamide works on peripheral μ-receptors in the gastrointestinal tract and does not exhibit analgesic properties due to poor penetration through the blood-brain barrier [1]. However, when taken at significantly higher than recommended doses, loperamide can exhibit central analgesic properties desirable to those seeking these opioid-like effects [7]. Recent reports have described the development of QTc interval prolongation and Torsades de Pointes, a type of ventricular tachycardia, after high-dose loperamide ingestions [1-6]. Given the wide availability of the medication and the potential for life-threatening cardiovascular toxicities, it is important that healthcare practitioners are aware of these risks.

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We report a case of high-dose loperamide ingestion resulting in QTc prolongation followed by ventricular tachycardia resulting in cardiac arrest, which, after standard resuscitation measures, was successfully managed by cessation of loperamide and an increase in the pacing rate of the patient's pacemaker.

Case Report

A 29-year-old female with a history of type III Ehlers-Danlos, history of drug abuse, anxiety, pituitary adenoma, first-degree atrioventricular (AV) block and left posterior fascicular block status-post pacemaker placement presented to our hospital's Emergency Department (ED) following one syncopal episode and two near-syncopal episodes that were preceded by hearing and vision changes. She had a history of opioid abuse but was previously tapered off of buprenorphine/naloxone and not taking any other medications for opioid use disorder. In the ED, she reported taking 75-100 tablets (150-200 mg) of loperamide daily for approximately 7 months prior to presentation, for self-management of withdrawal symptoms, as an opioid substitute. She reported having recent bowel movements and had no other complaints.

Her cardiac history dated back approximately 9 months prior to this presentation when she reported having similar syncopal episodes that resulted in an admission to the Coronary Care Unit. There she was found to have a monomorphic, wide-QRS tachycardia with a right bundle branch block (RBBB) morphology on electrocardiogram (ECG). Her QTc on that admission ranged from 435-485 ms in the setting of a QRS interval from 138-150 ms. The electrophysiology (EP) service was consulted and ultimately, the patient’s ECG was determined to show sinus rhythm first-degree AV block, RBBB, and left anterior fascicular block. A stress test showed 1:1 AV conduction at maximal heart rates and watchful waiting was recommended. She continued to experience pre-syncopal episodes and reported these to her outpatient physician. Her QTc at that time was 485 ms with a QRS duration of 160 ms. She was admitted a few days later for a tilt table test, which was negative, and an EP study. This study revealed that the patient had an HV interval of 112 milliseconds (normal 35-55 m sec [8]) with associated first degree AV block and left posterior fascicular block (LPFB). Due to her symptoms and the results of her EP study, the decision was made to implant a pacemaker. Of note, up to this point, the patient had not disclosed her loperamide use.

In the admission of interest, she was initially found to have a QTc of 616 ms and a QRS duration of 210 ms, along with 1st degree AV block (PR 250 ms) and LPFB. The EP team was consulted to interrogate her pacemaker. It was found to be working properly and had not sensed any arrhythmias. The patient’s urine toxicology screen was negative and electrolyte levels were normal. Activated charcoal was not administered given the patient’s self-reported chronic nature of loperamide abuse. The Poison Control Center and covering pharmacist were contacted. Upon literature review, it was determined that there was a possible link between loperamide and syncope and cardiac events.

The patient was transferred to a cardiac medicine floor and monitored with telemetry given the prolonged QTc. The following morning, she experienced sustained polymorphic ventricular tachycardia (VT) with spontaneous recovery. Her QTc was recorded as 680 ms (QRS 120 ms) and she was given a total of 6g of magnesium and transferred to the CCU for additional monitoring. Less than one hour after arrival to the CCU, she became unresponsive with polymorphic VT followed by ventricular fibrillation. Following cardiopulmonary resuscitation and defibrillation x1, she had return of spontaneous circulation and was awake and alert. EP was consulted and increased her pacemaker rate to 90 beats per minute. She continued to receive magnesium (range, 4-8g) and potassium (range, 20-100mEq) supplementation each day following cardiac arrest for goal potassium level >4.5 mEq/L and goal magnesium level of >2.5 mg/dL. The patient did not experience any further cardiac episodes during her inpatient stay and each day, her QTc and QRS durations became progressively shorter. She was ultimately discharged with the QTc <500 and a QRS duration of 82 ms after 7 days in the hospital. Upon later review, an assessment using the Naranjo algorithm, a method for determining the probability of a causal relationship between drug exposure and adverse drug reaction (ADR), yielded a score of 7, defined as probable ADR [9]. In our case, drug levels were not obtained and no rechallenge occurred.

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Results and Discussion

One-third of Americans admit to taking more than the recommended dose of an over the counter medication (OTC) and only half of patients read the labeling prior to using the medication for the first time [10]. OTC medications are labeled as such by the FDA due to their safety profile when used as recommended. This case report adds to the growing evidence that OTC medications, like loperamide, can carry significant health risks when not used appropriately.

Loperamide has been available for OTC purchase since 1988 [11]. Until recently, loperamide was generally thought to be without any significant side effects or high abuse potential given its rapid metabolism and poor penetration through the blood-brain barrier [12]. The lack of central effects at therapeutic doses is largely due to intestinal P-glycoprotein efflux pumps, which limit transluminal drug uptake and high first-pass metabolism. When ingested in high doses, studies have shown that loperamide may exert central effects due to saturation of P-glycoprotein transporters, CYP3A4 and CYP2C8, which results in an increase in drug concentrations [13]. This effect raises concern for the potential manipulation of loperamide drug-drug interactions to increase central effects. A recent case report depicts this concern in the potential abuse patterns of drug abusers with OTC medications. The report describes a 26-year-old male who presented with syncope and was found to have a QTc of >700 after ingestion of large dose of loperamide for several months. He had a history of drug abuse and through information sharing with other abusers had learned that taking loperamide with cimetidine, a known potent inhibitor of P-glycoprotein and CYP3A4, could produce opioid-like central nervous system effects [6].

The half-life of therapeutic doses of loperamide is between 9.1-14.4 hours, with a peak concentration within 2.5-5 hours and duration of action of nearly 24 hours [7]. However, the toxicokinetics of loperamide remain largely unknown. In our case, from the maximum-recorded QTc of 680m sec, it took nearly 100 hours for her QTc to drop below 500 m sec. This demonstrates the potential for significant pharmacokinetic changes following loperamide overdose.

At the time of this author’s literature search, 5 publications totaling 8 high-dose loperamide patient exposures and subsequent cardiac toxicities had been reported [1-6]; ours is now the 9th documented case. Most of these documented cardiac arrhythmias, including ours, have been life-threatening and most have occurred in patients ingesting high-dose loperamide for extended periods of time. Each of the patients had observed QTc prolongation, increasing their risk for Torsades de Pointes.

The case series published in 2014 by Marraffa, et al. highlighted the potential for life threatening cardiac arrhythmias that can occur with chronic loperamide abuse in patients without a cardiac history [1,2]. All five patients presented with cardiac conduction disturbances and three experienced life-threatening arrhythmias [1]. Two patients were successfully managed by placement of a transvenous pacemaker. Co-ingestion with methadone was tested in 4 of the cases and was not detected in any case. Only one case reported medication co-ingestion (amitriptyline) that may have contributed to QTc prolongation. Four of the cases revealed loperamide concentrations ranging from 22-130 ng/mL (therapeutic range 0.24-1.2 ng/mL [1]). Recurrence of cardiac arrest occurred in one patient following relapse; resolution of cardiac disturbances occurred following cessation of loperamide use in all 5 cases [1]. This case series has established a causal relationship between occurrence of cardiac arrhythmias and loperamide abuse.

Cardiac arrhythmias, such as Torsades de Pointes, can result from prolongation of the QT interval or electrolyte abnormalities, specifically potassium and magnesium [14]. Loperamide is structurally similar to haloperidol and is a synthetic opioid, as is methadone; both of these drugs have been shown to cause QTc prolongation. The precise mechanism of loperamide-induced QT prolongation is unknown. However, the QTc prolongation observed with other synthetic opioids has been postulated to be secondary to inhibition of the cardiac hERG potassium channel [15].

The potential treatment of loperamide-induced cardiac arrhythmias has not yet been extensively discussed. In the event of chronic abuse or acute ingestion, the use of a transvenous pacemaker or pharmacological pacing with isoproterenol has been described in previous cases. Loperamide is 97% protein bound and thus unlikely to be eliminated by hemodialysis [7]. Different from the previously reported cases, our patient had a pacemaker in place at the time of presentation. It should be noted, there is the possibility that her initial

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abnormal cardiac rhythm findings, which caused her to need a pacemaker, occurred while she was already consuming large doses of loperamide. Following two instances of life-threatening arrhythmias, one requiring defibrillation, our patient’s pacemaker pace was increased to 90 beats per minute. Similarly, three of the six previously reported cases received a transvenous pacemaker during their inpatient stay. Another, less invasive treatment strategy, is to increase heart rate pharmacologically by using isoproterenol. Two patients, including one in the original case series who relapsed, were paced with isoproterenol as a support measure [1,6].

There are two other management options that should be noted, activated charcoal and intravenous lipid emulsion (ILE). Activated charcoal has long been utilized as a method of gastrointestinal decontamination after potentially toxic ingestions. After oral administration, activated charcoal adsorbs chemicals, thereby preventing their systemic absorption and subsequent toxicities. Activated charcoal is most likely to benefit patients who present soon after ingestion, before toxins have been absorbed through the gastrointestinal tract. Thus, activated charcoal is generally considered to be of limited use after chronic or delayed presentation ingestions [16]. ILE were initially used to treat systemic toxicity of local anesthetics, but could be considered as a possible treatment option for any lipophilic drug toxicity. While loperamide does not cross the blood brain barrier due to the efflux pump noted above, it is a lipophilic drug and thus ILE could play a role in the toxic patient [17]. The mechanisms by which ILE provides benefit include the formation of a “lipid sink” as the lipophilic drug is surrounded and rendered nontoxic and also by providing a ready source of energy to myocardial cells [18]. A recent case report of a 25-year-old female taking large doses of loperamide and requiring extensive medical involvement, used ILE as part of her toxicity management [4].

**Conclusion**

Health care professionals are responsible for caring for patients in the acute setting. Collecting patient health histories by asking a multitude of questions can help clinicians determine the cause and ultimately the treatment that will meet the needs of the patient. It is critical for health care professionals to be aware of the life-saving treatments as noted above in the setting of acute ingestion of medications. Additionally, there is also the responsibility to inform the public about the potential detrimental effects of seemingly safe medications when used incorrectly. A recent study found that nearly one quarter of physicians do not directly ask patients about use of over the counter medications [10]. Given the potential for QTc prolongation and the increasing abuse of loperamide, there is great need for increased awareness of healthcare professionals. Especially in patients with a history of abuse, consideration of loperamide misuse in otherwise healthy patients who present with cardiac arrhythmias is warranted. Further investigation into the mechanism of QTc prolongation with loperamide is necessary.

**Conflict of Interest**

The authors have no conflicts of interest as it relates to this article.

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