Cardiac conduction disturbance after loperamide abuse


To cite this article: J. M. Marraffa, M. G. Holland, R. W. Sullivan, B. W. Morgan, J. A. Oakes, T. J. Wiegand & M. J. Hodgman (2014) Cardiac conduction disturbance after loperamide abuse, Clinical Toxicology, 52:9, 952-957, DOI: 10.3109/15563650.2014.969371

To link to this article: http://dx.doi.org/10.3109/15563650.2014.969371

Published online: 27 Oct 2014.
Cardiac conduction disturbance after loperamide abuse

J. M. MARRAFFA, M. G. HOLLAND, R. W. SULLIVAN, B. W. MORGAN, J. A. OAKES, T. J. WIEGAND, and M. J. HODGMAN

1Department of Emergency Medicine, Upstate Medical University, Syracuse NY, USA
2Department of Emergency Medicine, School of Medicine, Emory University, Atlanta, GA, USA
3Department of Emergency Medicine, URMC and Strong Memorial Hospital, Rochester NY, USA
4URMC and Strong Memorial Hospital, Ruth A. Lawrence Poison and Drug Information Center, Rochester, NY, USA

Context. Prescription opioid abuse is a major public health concern and an ongoing epidemic in the United States. Loperamide is a widely available and inexpensive over-the-counter antidiarrheal with peripheral mu-opioid receptor activity. Online resources discuss the use of loperamide for the amelioration of withdrawal symptoms or recreational abuse. We describe the clinical course of 5 patients abusing loperamide, 3 of whom had life-threatening cardiac arrhythmias.

Methods. In this observational case series, patients with cardiac arrhythmias or history of loperamide abuse with cardiac arrhythmias were identified; 5 patients were identified and 4 of the 5 patients were seen directly at the bedside. Clinical profile and outcome of patients is reported. Results. We report 5 patients with history of loperamide abuse; 3 of the 5 patients had life-threatening cardiac arrhythmias. One of the patients experienced a second life-threatening arrhythmia after he resumed loperamide abuse. Loperamide levels were obtained in 4 of the 5 patients and were at least one order of magnitude greater than therapeutic concentrations. Discontinuation of loperamide resulted in complete resolution of cardiac conduction disturbances. Conclusion. This case series describes several patients with cardiac conduction abnormalities and life-threatening ventricular arrhythmias temporally related to loperamide abuse. With the recent efforts to restrict the diversion of prescription opioids, increasing abuse of loperamide as an opioid substitute may be seen. Toxicologists should be aware of these risks and we urge all clinicians to report such cases to FDA Medwatch®.

Introduction

Prescription opioid drug abuse is a major public health concern and an ongoing epidemic in the United States. According to the Centers for Disease Control and Prevention (CDC), unintentional poisoning is the leading cause of accidental death in the US and prescription opioid analgesics are the most commonly involved drug in accidental poisoning deaths.1 Numerous efforts are currently being made to decrease the availability of prescription opioids and to minimize misuse, abuse, and diversion, including electronic prescription drug monitoring programs.1 Such restrictions are likely to lead to an increase in the use of illicit opioids, such as heroin, as well as the use of alternative pharmaceuticals and naturopathic preparations.2

Loperamide is a widely available and inexpensive over-the-counter antidiarrheal with peripheral mu-opioid receptor activity. Online resources discuss the use of loperamide for the amelioration of withdrawal symptoms or recreational abuse.3 We report novel clinical effects associated with ingestions of high doses of loperamide. We describe the clinical course of 5 patients abusing loperamide, 3 of whom experienced life-threatening cardiac arrhythmias associated with toxic loperamide concentrations.

Methods

Patients and samples

This is an observational case series of patients whom the authors consulted through either poison center consultation or direct bedside treatment. The patients were identified by the treatment providers as having cardiac arrhythmia or history of loperamide abuse with concurrent cardiac abnormalities. Case 1 was the index case and the authors (JO and BW) were involved in the management only through poison center consultation. Cases 2, 3, 4 (JM, MJH, MGH, and RWS), and 5 (TW) were all seen directly at the bedside. The poison center records (Case 1) and hospital records (remainder of cases) were reviewed by the authors. The Investigational Review Board of Upstate Medical University deemed this to be exempt.

Case details

Case 1

A previously healthy 30-year-old male presented to a local emergency department after multiple syncopal episodes.

Received 15 May 2014; accepted 21 September 2014.

Address correspondence to Dr. Jeanna M. Marraffa, Department of Emergency Medicine, Upstate New York Poison Center, SUNY Upstate Medical University, 750 East Adams Street, Syracuse, NY 13210, USA. E-mail: marraffj@upstate.edu
He had no known medical history and was not taking any known chronic medications. He had experienced 2 episodes on the day of presentation. In the emergency department he was hemodynamically stable with a regular pulse of 50–60 beats per minute (bpm). Initial electrocardiogram (ECG) showed a wide QRS and a QTc of over 500 ms. The initial rhythm was interpreted as an accelerated idioventricular rhythm (Fig. 1). The patient’s electrolyte levels were normal (Table 1). He was admitted to the cardiology service. His hospital course was complicated by several episodes of polymorphic ventricular tachycardia and cardiac arrest with successful resuscitation on hospital day 1. Subsequent cardiac catheterization and electrophysiology studies were unremarkable. Over the course of his hospitalization, his conduction disturbances resolved. At discharge his ECG showed only T wave inversions over the precordium. At follow-up after one month, he had a normal ECG.

While hospitalized, the patient admitted to escalating use of up to two hundred tablets of loperamide, 2 mg each, daily for several weeks as an opioid alternative. A loperamide serum concentration measured on hospital day 2 was 22 ng/mL 3 days after last loperamide use (therapeutic loperamide concentrations are 0.24–1.2 ng/mL 4).

A comprehensive serum toxicology screen performed on admission was negative (the exact analytical methodology used is unknown).

Case 2

A 43-year-old female presented to the emergency department after syncope. She had a history of opioid abuse and was on no chronic prescription medications. In the emergency department, she experienced multiple episodes of torsades de pointe (TdP) that were refractory to lidocaine, amiodarone, sodium bicarbonate, magnesium, and fatty acid emulsion (lipid rescue therapy), as well as repeated cardioversion (over 15 shocks). When she was not experiencing TdP, she was awake and alert and in fact, described a prodromal feeling immediately before TdP recurred. Control was ultimately achieved by transvenous pacemaker insertion with overdrive pacing. An initial ECG on presentation revealed a sinus rhythm with a QRS of 130 ms and QTc (by Bazett) of 684 ms with frequent PVCs. A copy of this ECG is not available. Overdrive pacing was continued until hospital day 3. During her hospitalization, she reported the use of 144 tablets of loperamide (2 mg daily) to manage opioid withdrawal. At discharge, on hospital day 5, her ECG showed a sinus rhythm with a QRS of 98 ms and QT/QTc of 462/421 ms. This was similar to an ECG from a previous hospitalization that preceded her abuse of loperamide (Figs. 2 and 3).

A loperamide serum concentration was not measured. Urine drugs-of-abuse immunoassay screen on admission was negative for opiates and methadone. The patient’s electrolyte levels are listed in Table 1. A subsequent outpatient electrophysiology evaluation found no underlying conduction abnormality.

Case 3

A 28-year-old male was admitted with syncope and recurrent wide complex tachycardia. His history included Crohn’s disease, substance abuse, and a hospitalization one year earlier for unexplained syncope. His medications were amitriptyline (his exact dose was unclear) and loperamide. His ECG on admission to the intensive care unit (ICU) showed a sinus rhythm with a rate of 56 bpm, QRS of 162 ms, and QT/QTc of 670/647 ms. Electrolyte levels were unremarkable (Table 1). He experienced both sustained and non-sustained pulseless ventricular tachycardia that were

<table>
<thead>
<tr>
<th>Patient</th>
<th>Potassium (mEq/L) [3.5–5.0]</th>
<th>Calcium (mg/dL) [8.5–10.8]</th>
<th>Magnesium (mEq/L) [1.5–2.2]</th>
<th>TSH mIU/L [0.3–5.0]</th>
<th>Methadone immunoassay</th>
<th>Loperamide concentration (ng/mL)^</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.0</td>
<td>9.4</td>
<td>1.8</td>
<td>N/A</td>
<td>Negative</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>3.6</td>
<td>9.4</td>
<td>2.6^×</td>
<td>0.963</td>
<td>Negative</td>
<td>N/A</td>
</tr>
<tr>
<td>3 a</td>
<td>3.2</td>
<td>8.7</td>
<td>2.5</td>
<td>1.620</td>
<td>Negative</td>
<td>130</td>
</tr>
<tr>
<td>3 b</td>
<td>4.0</td>
<td>9.6</td>
<td>1.4</td>
<td>N/A</td>
<td>N/A</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>3.5</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>3.2</td>
<td>9.0</td>
<td>1.7</td>
<td>N/A</td>
<td>Negative</td>
<td>33</td>
</tr>
</tbody>
</table>

^Denotes abnormal laboratory value.
Values in brackets [ ] are reference range.
X: received magnesium sulfate prior to drawing blood.
:^: therapeutic range: 0.24–1.2 ng/mL^1.
N/A: denotes not available/not provided.
3a and 3b are presentations 1 and 2, respectively, for Case 3.
QTc remained greater than 500 ms until hospital day 10. A follow-up ECG one month later, when no longer taking loperamide, showed a sinus rhythm with a QRS of 102 ms and a QT/QTc of 360/435 ms. An ECG from 2008, prior to his loperamide abuse, showed a sinus rhythm with a normal QRS and QT/QTc of 382/443 ms (Fig. 4).

He reported escalating use of loperamide to over 396 loperamide 2-mg tablets (792 mg daily). A serum loperamide concentration measured 5 h after presentation was 130 ng/mL; other tests included an amitriptyline concentration of 100 ng/mL and nortriptyline of 82 ng/mL (therapeutic, total TCA: 100–250 ng/mL). Screening for both methadone and quinine were negative. Urine drugs-of-abuse immunoassay screen was negative for all 9 substances tested. He disclosed that he had also been abusing loperamide 1 year earlier when he had been hospitalized for unexplained syncope.

One year after our initial consultation, he suffered a cardiac arrest while undergoing surgery for complications of his Crohn’s disease. Operating room rhythm strips were not recorded and were unavailable; however, conversation with the anesthesiologist caring for the patient revealed that he had a prolonged QTc and deteriorated into TdP which responded to defibrillation. The surgery was immediately terminated and his abdomen was packed and remained open, and he was transferred to the surgical ICU. He was pharmacologically paced using an isoproterenol infusion (2 mcg/min) for approximately 24 h with no further episodes of TdP. Review of pre-operative ECG showed sinus rhythm with a rate of 63 bpm, QRS of 166 ms, and QT/QTc of 584/597 ms. After the isoproterenol infusion was discontinued, ECG showed a sinus rate of 62 bpm, QRS of 134 ms, and QT/QTc of 388/383 ms. After he was extubated, he admitted to recurrent loperamide abuse of forty of the 2-mg tablets daily (80 mg daily). He had been on methadone for pain several months earlier, but denied any methadone use for the previous 2 weeks. A loperamide level submitted on the day of the cardiac arrest returned at 97 ng/mL. Although requested, a methadone concentration was unfortunately not measured, so we could not confirm his history. He subsequently underwent a complete cardiac electrophysiology evaluation with normal findings.

### Case 4

A 33-year-old male presented to the hospital with complaints of shortness of breath after ingesting 60–100 tablets of loperamide (2 mg) over the previous 6 h as an opioid substitute. He states that he normally uses loperamide but took more than usual on this occasion. His exact chronic loperamide dose is unclear. He had no significant medical history and was not on any chronic medications. His vital signs included a heart rate of 79 bpm; blood pressure of 139/88 mmHg; respiratory rate of 18 breaths/minute, and 100% saturation on room air. Physical examination was only significant for miosis. ECG revealed sinus rhythm with a QRS of 128 msec and QT/QTc of 566/636 msec. Electrolyte levels were normal (Table 1). Sodium bicarbonate and magnesium sulfate, as well as 40 mEq intravenous potassium chloride were administered. There was no change in QRS despite intravenous administration of 3 ampules of sodium
bicarbonate. The patient remained hemodynamically stable. Twelve hours later, his rhythm remained sinus with a QRS of 124 ms and QTc of 599 ms. At 24 h, his ECG was sinus with a QRS of 100 ms and QTc 409 ms. A serum loperamide level measured on presentation was 77 ng/mL. No other toxicology testing was performed during the hospitalization. The patient left against medical advice 24 h after presentation and no further follow-up was available.

Case 5

A 33-year-old male presented to the emergency department with anxiety, panic, and chest tightness. He had a history of opioid and ethanol abuse, and had recently been abusing loperamide—thirty-five of the 2-mg tablets daily for months. He had no significant medical history and was not on any chronic medications. On the day of presentation, he had taken 140 mg of loperamide over the previous 7 h. He was hemodynamically stable with blood pressure of 118/87 mmHg, heart rate of 102 bpm, respiratory rate of 16 breaths/minute, and 97% saturation on room air. An ECG showed a sinus rhythm with a rate of 84 bpm, QRS of 118 msec, and QTc of 490 msec. Electrolyte levels showed a potassium of 3.2 mEq/L, but were otherwise unremarkable (Table 1). He received potassium supplementation as well as magnesium intravenously, and benzodiazepines for concern of ethanol withdrawal. No arrhythmias were observed and he was discharged the next day with sinus rhythm with a QRS of 92 ms and QT/QTc of 448/450 ms. The loperamide concentration submitted on admission was 33 ng/mL. Urine drugs-of-abuse immunoassay screen was negative for methadone and opiates, and only positive for benzodiazepines (obtained after administration of lorazepam) and Tetrahydrocannabinol (THC).

Discussion

We report 5 patients who presented to hospitals with cardiac conduction disturbances, and 3 of them had
life-threatening arrhythmias in the setting of loperamide abuse. In 4 patients, loperamide concentrations were measured and all had supratherapeutic concentrations. Case 3 experienced a second life-threatening arrhythmia after he resumed loperamide abuse. With cessation of loperamide, the conduction disturbances in all 5 of these patients resolved. Cases 2 and 3 subsequently had complete electrophysiology evaluation without any underlying cardiac conduction abnormalities. Illustrative electrocardiograms and rhythm strips are found in Figs. 1–5.

We observed both QRS and QT prolongation, and both monomorphic and polymorphic (TdP) ventricular arrhythmias. Loperamide has not previously been reported as a cause of cardiac conduction disturbances, and the mechanism whereby loperamide may lead to these disturbances at these supratherapeutic doses is unknown. QRS prolongation is usually due to delays in depolarization (such as sodium channel blockade), while QT prolongation reflects delays in repolarization (such as block of slow potassium rectifying current, Ikr). Simulated modeling data suggest that loperamide is an inhibitor of the HERG-coded Ikr channel. We theorize that this is a dose-dependent phenomenon: concentrations of loperamide after therapeutic concentrations will not result in QT prolongation, but after massive excessive dosing or in large overdoses, the risk of QT prolongation and ventricular arrhythmias presents due to higher drug concentrations at the Ikr channel. Several Vaughan-Williams 1A anti-arrhythmics possess both sodium channel antagonism leading to QRS prolongation and Ikr block that may result in QT prolongation. We also observed that at very high concentrations, loperamide may also have effects on cardiac sodium channels leading to the QRS prolongation. Unfortunately, there is a paucity of evidence-based literature describing the cardiac effects of loperamide.

Loperamide is a peripherally acting opioid agonist effectively excluded at the blood–brain barrier by p-glycoprotein. After routine therapeutic loperamide doses, peak concentrations are seen within 2.5–5 h. The half-life of loperamide is 9.1–14.4 h. Therapeutic doses of loperamide (2 mg and 8 mg doses) yield serum concentrations of 0.24 and 1.2 ng/mL within 5 h, respectively. In Case 3, we observed very prolonged duration of the cardiac conduction disturbances. This may reflect a persistent gut burden with ongoing absorption. We did not observe such a prolonged course in any of the other patients. The toxicokinetics of loperamide have not been reported. In our patients who had confirmatory loperamide concentrations, these concentrations were at least one order of magnitude greater than therapeutic concentrations.

We cannot definitively rule out that a co-ingested drug may be responsible for either the QRS or QT prolongation. Methadone was specifically assayed for in 4 cases [Cases 1,2,3 (first admission) and 5] and was not detected. Quinine, a p-glycoprotein inhibitor, has been suggested on some online forums as a method to enhance passage of loperamide into the central nervous system. We did not detect quinine in the 3 cases, where we looked for this drug. Case 3 (first admission) was also on a tricyclic antidepressant (TCA) and although his concentration of total TCA was within the accepted therapeutic range, this may have contributed to the observed QRS prolongation.

We did not specifically ask any of these patients how they had discovered the abuse potential of loperamide. The use of loperamide, both singularly at high doses, and in combination with p-glycoprotein inhibitors, is widely discussed on online forums and blogs. Loperamide first appeared on these sites in 2005, with a dramatic increase in the number of mentions of loperamide since 2010. It is primarily described as a remedy for opioid withdrawal. Numerous
sites also discuss its recreational use as an opioid substitute. Daniulaityte et al.\(^3\) report that the doses used range from 70 to 200 mg per day. Nearly 70% of posts describe its benefit for withdrawal and 25% report the potential of loperamide to produce pleasurable effects.\(^3\)

We are unaware of any previous reports on an association of loperamide toxicity with cardiac arrhythmias (Case 1 was previously presented as an abstract at NACCT 2004\(^{10}\)). We performed an FDA Medwatch\(^\circ\) query through December 2012 which revealed only 3 other cases of ventricular tachycardia, arrhythmia, or death reported with loperamide as the sole substance. Berger et al.\(^{11}\) identified only 1 case reported to the FDA Adverse Event Surveillance System (AERS) with loperamide-induced QT prolongation.

There are a number of limitations to this case series. We acknowledge that this is an association and that this does not definitively demonstrate causality. This is an anecdotal report of 5 patients who either were directly cared for by us (Cases 2–5) or through the poison center (Case 1). We cannot definitively exclude co-ingestion of another drug affecting cardiac conduction, but all cases denied other medications. We did not have comprehensive drug testing in most cases. Formal electrophysiologic studies were performed in only 2 cases, although both of these patients suffered life-threatening arrhythmias and neither had any evidence of an underlying conduction abnormality or ion channelopathy after loperamide had been discontinued. The temporal relationship of excessive loperamide use with conduction disturbances as well as arrhythmias in several cases (with extremely high serum concentrations when assayed), positive recurrence with re-challenge (Case 3), and the resolution of the conduction disturbances during hospitalization all strongly suggest a causal relationship.

**Conclusion**

This case series describes several patients with loperamide abuse temporally associated with cardiac conduction disturbances and life-threatening ventricular arrhythmias. Although loperamide is generally safe at therapeutic doses, supratherapeutic doses of loperamide may place patients at risk for life-threatening cardiac arrhythmias. In this case series, standard anti-arrhythmic medications were ineffective in treating the arrhythmias, and only electrical overdrive pacing or isoproterenol continuous infusion were effective in preventing further episodes of TdP.

With the recent efforts to restrict the diversion of prescription opioids, increasing abuse of loperamide as an opioid substitute may be seen. Toxicologists should be aware of the risks of loperamide toxicity, and we urge all clinicians to report such cases to FDA Medwatch\(^9\).

**Declaration of interest**

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

**References**