CASE REPORT

A Heart-Wrenching Case of Loperamide Toxicity

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Abstract

Background: Loperamide is an insoluble meperidine analog that is commonly used for diarrhea. It is an inexpensive and frequently available over the counter drug. While physicians are aware of its opioid effects, Loperamide use is also linked to cardiac conduction disturbances.
Case presentation: We present a case of Loperamide toxicity with QRS, Corrected QT interval (QTc) prolongation and ventricular arrhythmias such as ventricular tachycardia leading to cardiopulmonary resuscitation (CPR). The patient survived and was evaluated to have prolonged QT interval. He later disclosed over the counter (OTC) and continued a regular use of Loperamide as an anti-diarrheal agent. During the rest of hospital stay, serial Electrocardiograms (ECGs) showed improvement in QT interval and patient was successfully discharged.
Conclusion: Loperamide inhibits intestinal peristalsis through its peripheral μ-opioid receptor agonism, as well as calcium channel blockade. Loperamide abuse is increasing, as patients use it either to experience euphoric effects or to attenuate the effects of opioid withdrawal. At high doses, Loperamide blocks cardiac sodium and potassium channels, resulting in prolonged QRS and QT intervals which can proceed to cardiac rhythm disturbances. Our case shows the acute and delayed cardiac effects of Loperamide toxicity which the treating physician should be made well aware of.

Keywords: Cardiac Toxicity; Loperamide; Ventricular Tachycardia

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INTRODUCTION

Loperamide is widely known as “poor man’s methadone” and medical toxicologists are familiar with its toxicity, but this has not spread as much to other clinical specialties. Loperamide is a μ-opioid agonist with poor oral bioavailability which is primarily used as an anti-diarrheal. Central nervous system (CNS) effects are limited when p-glycoprotein (P-GP) is functioning normally at the blood-brain barrier. In massive (>50-100 times the usual dose) of Loperamide ingestions, the P-GP becomes overwhelmed leading to expected opioid CNS effects. Loperamide poisonousness cannot be portrayed by its narcotic impacts alone. Different instances of heart poisonousness have been issued in new research, some of which being lethal (1). Indications of loperamide poisonousness incorporate palpitations, sickness and spewing, tension, total fatigues, pre syncope, dyspnea, new-beginning or repetitive syncope, diminished degree of cognizance, seizure-like reaction and heart failure. It is essential to give close consideration to the heart impacts identified with loperamide poisonousness. ECG ought to be assessed for heart dysrhythmias and delayed QRS/QT interims. Manifestation of rhythms differs, yet incorporates ventricular tachycardia/fibrillation, asystole, junctional escape rhythm rate and Torsade de pointes. Serum electrolytes ought to be assessed for reversible elements for QT-interim prolongation, (including potassium deficiency, magnesium deficiency) and co-intakes.

Loperamide misuse so as to get high or for self-control of withdrawal usually happens at high dosages. CYP and P-GP stoppers are usually ingested together to expand loperamide plasma agglomerations. CYP3A4 and CYP2C8 stoppers increment the plasma centralization of loperamide by around two- and fourfold, separately and by more than twelvefold when the two compounds are repressed all the while. P-GP stoppers additionally increment the plasma centralization of loperamide by around two- to threefold and can likewise expand the loperamide CNS centralization by its negative impacts on the BBB (4). For instance, some addicts consume cimetidine and grapefruit juice together to hinder CYP compounds, or black pepper and quinidine to repress P-GP (2-5).

Loperamide poisonousness control is to a great extent strong and ought to be accompanied by sterilization, disposal, counteractants, and steady consideration together with examinations by the poison control center in the neighborhood.

CASE REPORT

A 30-year-old male with epilepsy and a history of

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taking loperamide for last 3-4 months for diarrhea was brought to the emergency room with generalized tonic-clonic seizures. Initial vital signs were heart rate at 100 beats per minutes, blood pressure 140/80 mmHg, temperature 37 degrees centigrade, oxygen saturation 95% on room air and point-of-care blood glucose of 200 mg/dl. On physical exam, he was somnolent, diaphoretic and had bilaterally reactive pupils. Laboratory tests were normal. In resuscitation room, the Cardiac monitor showed Torsades de pointes with hemodynamic instability. For airway protection, patient was intubated and received IV magnesium and IV amiodarone. Urine toxicology screen was unremarkable except for benzodiazepine as a result of IV Midazolam which he received during intubation for sedation. Electrocardiogram (ECG) showed prolonged QT interval and Corrected QT Interval (QTc) of 600 msec. He had episode of Ventricular Tachycardia (VT) that later transformed into pulseless electrical activity (PEA) for which cardio pulmonary resuscitation (CPR) and synchronized cardioversion were performed until the return of spontaneous circulation (ROSC) was achieved. He was intubated and shifted to the medical ICU. Cardiology team was taken on board as he had prolonged QT interval. Temporary pacemaker (TPM) was placed due to persistent arrhythmias. Serum electrolytes were unremarkable. Complete blood counts, renal functions and serum troponin levels were well within normal limits. Magnetic Resonance Imaging (MRI) of the brain was unremarkable. He was extubated and TPM was removed. After extubation, patient remained stable, however, the patient admitted himself that he had been self-medicating with over-the-counter (OTC) Loperamide for diarrhea for the past 3-4 months. Patient denied using any other illicit drug. Serial ECG monitoring showed gradual decrease in QTc. Patient was instructed not to use Loperamide again. He remained stable hence was discharged.

DISCUSSION

Early 1980s reports felt that Loperamide had low abuse potential but more recently it has been described in large doses as “Poor Man’s Methadone” to avoid opioid withdrawal, or to achieve a psychoactive effect. In early 2010, reports arose among toxicologists of severe cardiac toxicity following massive Loperamide ingestions. At supratherapeutic concentrations, Loperamide inhibits cardiac fast Sodium (Na) channels and The Human Ether-a-go-go-related Gene (HERG) Potassium (K) channels, resulting in wide QRS and prolonged QTc which can progress to malignant ventricular dysrhythmias (3). Patients may present with recurrent syncope or cardiac arrest. Most concerning may be the incredibly prolonged QTc (frequently noted as >680msec). It is reasonable to normalize all cations (K, Ca, Mg), and get prepared for arrhythmias especially Torasades. Tachycardia protects against torsades, so one may consider overdrive pacing via drugs/electricity. The natural effect of Loperamide would be to delay its own gut absorption, plus there may be history of deliberate co-ingestion intended to decrease metabolism.

Prior to 2011, the risk of cardiac toxicity secondary to Loperamide use was not recognized, largely because it is not seen with therapeutic dosing. And interestingly, single acute overdoses of Loperamide have not resulted in cardiac toxicity. The cardiac toxicity cases reported in the medical literature usually involve excessive chronic dosing (3-6). Although there have been reports of both QRS widening and QTc prolongation, QTc prolongation is more commonly reported. There have even been reports of bradycardia suggesting a direct myocardial depressant effect (4).

After the first reports of cardiac toxicity, the quest to identify the mechanism of toxicity began. The data are scarce and generally are in vitro data; although there are some animal models being done with the data yet to be published. Loperamide, and to a lesser degree N-desmethyl Loperamide (DLOP), block cardiac Na-channels. The primary culprit in deaths though is in their ability to block the K-channel. Loperamide concentrations of 40 nmol/L (much higher than concentrations achieved at therapeutic doses) inhibit the HERG channel to half of its activity. As the concentration of Loperamide increases, the blockade of the HERG channel increases (7).

A dose-response curve for cardiac toxicity has not been defined, however the cases described in the literature report elevated serum concentrations of several fold higher than the expected therapeutic serum concentrations (3).

A recent review of the FDA Medwatch system from 1976 through December 2015 described 48 cases of Loperamide abuse with serious cardiac events and 10 deaths. The median daily dose of Loperamide in these cases were 250 mg (range: 70-1600 mg). Even more interesting is that only 4 cases reported concurrent use of a P-GP or CYP 3A inhibitor further strengthening that the P-GP efflux pump can be overwhelmed with excessive doses (4).

Management includes:

1. Sterilization: Loperamide is probably taken in by initiated charcoal. Loperamide amounts are diminished ninefold following the addition of actuated charcoal. Top amount is reached in 5 hours following the intake; subsequently, diminishing the intestine motions implies that one ought to consider broadening the possibility of when actuated charcoal would be proper after about an hour (4).

2. Improving disposal: No information exists on whether actuated charcoal or entire intestine liquid circulation would better the loperamide disposal. There exists no logical proof on loperamide being evacuated by dialysis to improve the omission of poisons.

3. Counteractant treatment: Naloxone ought to be administered when the respiration is depressed and continued dosing might be required. To forestall the chance of hastened narcotic withdrawal, the most minimal compelling portion of naloxone ought to be administered so as to maintain a strategic distance from hazardous difficulties, including seizures and arrhythmias (5-10). Sodium bicarbonate IV may fight the heart-related poisonous impacts of loperamide, particularly the sodium blockage. On the off chance that sodium bicarbonate is utilized, make certain to much of the time screen serum electrolytes.

4. Steady consideration: Reverse any electrolyte variations from the norm (calcium deficiency, potassium deficiency, magnesium deficiency). Heart’s abnormal sequence of electrical impulses have all been effectively

cured through controlled electric shocks. They may need to be continued, as there was a report on a case that needed over 15 tries to bring back the normal rhythm (6-9). Magnesium, Amiodarone, Lidocaine and Overdrive pacing are advised to be utilized. Extracorporeal life support is a possibility for some patients with cardiac and circulatory failures concerning every single therapeutic treatment.

Since both loperamide and DLOP are Na-blockers, sodium bicarbonate may be helpful. However, the few case reports describe inefficacy of sodium bicarbonate in narrowing the QRS complex duration (10-14). In a patient with QRS widening, sodium bicarbonate 1-2 meq/kg as an intravenous bolus should be attempted. It is imperative to follow serum potassium levels closely and replace them to a normal range in a patient receiving sodium bicarbonate as hypokalemia contributes to and worsens the degree of QTc prolongation and can make cardiovascular toxicity worse.

How long should we expect these patients to be symptomatic? After reviewing the pharmacokinetic properties of Loperamide and its metabolite, worst case scenario half-life of up to 11 hours and employing the 'rule' of 3-5 half-lives for a drug to be fully eliminated from the body. Unfortunately, the kinetics of these super high doses of Loperamide are unknown.

Compared to the public health crisis of abusing other opioids, the incidence of Loperamide misuse and abuse is comparatively low. Despite the low incidence, the risk of severe cardiac toxicity is high and when compared to other opioids, it has a high probability of causing severe cardiac effects (13).

More research is needed to answer so many unknowns. Being aware of this new trend is important and in patient, particularly those with opioid use disorder, with unexplained syncope or abnormal ECG, one may want to think and ask about Loperamide abuse.

CONCLUSION

This case illustrates the acute and delayed cardiac effects of Loperamide toxicity; recognizing and treating the lethal complications of which are paramount.

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