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Not your regular high: cardiac dysrhythmias caused by loperamide

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ABSTRACT

Objective: Loperamide, a non-prescription anti-diarrheal agent, is a peripheral mu-opioid receptor agonist that is excluded from the blood-brain barrier by p-glycoprotein at therapeutic doses. Overdoses of loperamide penetrate the central nervous system (CNS), leading to abuse. We report cardiac conduction abnormalities and dysrhythmias after ingestion of a recreational supra-therapeutic dose of loperamide confirmed with an elevated blood loperamide concentration. Case details: A 48-year-old woman with a history of alcohol and benzodiazepine abuse presented to the emergency department (ED) with somnolence, weakness and slurred speech. She was taking 20 to 40 tablets of 2 mg loperamide 1–2 times/day for weeks along with clonazepam and whiskey. Vital signs were: blood pressure (BP), 124/90 mmHg; heart rate (HR), 88/min; respiratory rate (RR), 20/min; T, 36.9°C; O2 saturation 100% on room air (RA). Glucose was 6.4 mmol/L. Electrocardiogram (ECG) had a ventricular rate of 58/min, QRS 164 ms, QT 582 ms with no discernable p-waves. Lactate was 3.5 mmol/L and potassium was 6.2 mEq/L. Labs were notable for an anion gap of 20 mEq/L, ethanol of 3.9 mmol/L, creatinine of 2.3 mg/dL and loperamide concentration of 210 ng/mL (average therapeutic plasma concentration 1.2 ng/mL). She became hypotensive, but responded to fluids. Following treatment for hyperkalemia with calcium, insulin, dextrose, and hypertonic sodium bicarbonate a repeat ECG had a ventricular rate of 66/min, QRS 156 ms, and QT 576 ms. Magnesium was given and pacer pads were placed. During the infusion of magnesium, her BP fell to 92/58 mmHg with a HR of 54/min, RR 14/min, O2 saturation of 97% on RA so the infusion was stopped. The ECG after the magnesium infusion had a ventricular rate of 51/min, QRS of 134 ms, and QT 614 ms. In the ICU she had multiple runs of non-sustained ventricular tachycardia that did not require therapy. Over the next 48 h she improved and was transferred to a floor bed. On day four of hospitalization the patient left against medical advice. At that time, her ECG showed sinus tachycardia with a heart rate 114/min, QRS 82 ms, QT 334 ms. Discussion: Loperamide produces both QRS and QT prolongation at supra-therapeutic dosing. A blood loperamide concentration of 210 ng/mL is among the highest concentrations reported. Supra-therapeutic dosing of loperamide is promoted on multiple drug-use websites and online forums as a treatment for opioid withdrawal, as well as for euphoric effects. With the current epidemic of prescription opioid abuse, toxicity related to loperamide, an opioid agonist that is readily available without a prescription is occurring more frequently. It is important for clinicians to be aware of the potentially life-threatening toxicity related to loperamide abuse in order to provide proper diagnosis, management and patient education.
Previous case reports and one case series describe patients with conduction disturbances and life-threatening ventricular dysrhythmias after supra-therapeutic loperamide dosing.[7–10] Cardiac complications from loperamide abuse are a relatively new finding and remain largely unknown in the medical community. This case describes cardiac conduction abnormalities and dysrhythmias that occurred after ingestion of a recreational supra-therapeutic dose of loperamide confirmed with an elevated blood loperamide concentration.

**Case details**

A 48-year-old woman with a history of alcohol and benzodiazepine abuse presented to the emergency department (ED) with somnolence, weakness, and slurred speech after her daughter found her at home confused. She was taking 20 to 40 tablets of 2 mg loperamide 1 to 2 times a day for several weeks along with clonazepam, and whiskey. The patient admitted that the use of loperamide was not for diarrhea but rather to “get a high”.

Vital signs were: blood pressure (BP), 124/90 mmHg; heart rate (HR), 88/min; respiratory rate (RR), 20/min; T, 36.9°C; O₂ saturation 100% on room air (RA), serum glucose was 6.4 mmol/L. Electrocardiogram (ECG) had a ventricular rate of 58/min, QRS 164 ms, QT 582 ms with no discernable p-waves (Figure 1). The QT interval is reported uncorrected with a paired heart rate in all instances. Lactate was 3.5 mmol/L and a rapid point of care iSTAT® potassium was 6.2 mEq/L. Other laboratory studies were notable for an anion gap of 20 mEq/L, magnesium 1.5 mg/dL, calcium 9.9 mg/dL, ethanol concentration of 3.9 mmol/L, and a creatinine of 2.3 mg/dL increased from a baseline of 0.8 mg/dL. Of note, the initial serum potassium concentration sent to the laboratory was 4.8 mmol/L. Although the iSTAT rapid point of care sample resulted first, both samples were drawn at the same time upon patient presentation, which suggests that the initial iSTAT® potassium concentration may have been falsely elevated. The patient’s loperamide concentration was 210 ng/mL (average therapeutic plasma concentration 1.2 ng/mL).[11]

Within fifteen minutes of presentation to the ED the patient became hypotensive with a BP, 85/53 mmHg and HR, 66/min. After 2 L of fluid the patient’s vital signs improved to: BP, 118/62 mmHg; HR, 67/min; RR, 15/min; O₂ saturation 96% on RA. The patient was treated for hyperkalemia with intravenous calcium gluconate 2 g, insulin 10 Units, 50% dextrose 50 mL, and 8.4% hypertonic sodium bicarbonate 25 mL. The repeat ECG had a ventricular rate of 66/min, QRS 156 ms, QT 576 ms (Figure 2).

Magnesium 1 gram IV was given and transcutaneous pacemaker pads were applied. During the infusion of magnesium, her BP fell to 92/58 mmHg with a HR of 54/min, O₂ saturation 97% on RA, so the infusion was stopped. The ECG after the magnesium infusion had a ventricular rate of 51/min, QRS of 134 ms, and QT 614 ms (Figure 3).

In the ICU she had multiple runs of non-sustained ventricular tachycardia (Figure 4) not requiring intervention. Over the next 48 h she improved and was transferred out of the ICU to a regular bed with telemetry monitoring. Pacing was not required. Electrolytes remained within normal limits and the patient had no further dysrhythmias. On day four of hospitalization, the patient left against medical advice. At that time, her ECG showed sinus tachycardia at 114/min, QRS 82 ms, and QT 334 ms (Figure 3).

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**Discussion**

At therapeutic dosing cardiac conduction abnormalities and dysrhythmia are not reported with loperamide use, thus it is
theorized that the cardiac effects observed are a dose-dependent phenomenon occurring only at supra-therapeutic dosing. The blood loperamide concentration of 210 ng/mL found in this patient is the highest measured concentration in a patient who did not expire reported on review of the medical literature. She reported taking between 40 to 160 mg of loperamide daily in divided doses to achieve her desired clinical effect, which is consistent with previously published doses of abuse. Daniulaityte et al. described daily average doses of 70 mg/day with some doses ranging up to 200 mg per day reported by loperamide abusers in posts from a website focused on illicit opioid use.\[4\]

The mechanism by which loperamide abuse leads to conduction abnormalities is currently unknown. The majority of patients described in the literature demonstrate both QRS complex and QT interval prolongation. While there is evidence that loperamide blocks cardiac potassium channels\[12\] and smooth muscle calcium channels\[13\] we speculate that effects on cardiac sodium channels are responsible for QRS widening.

![Figure 2. ECG taken after treatment with intravenous calcium gluconate 2 g, insulin 10 Units, 50% dextrose 50 mL, and 8.4% hypertonic sodium bicarbonate 25 mL approximately 1.5 h after arrival to the ED. Demonstrates ventricular rate of 66/min, QRS 156 ms, QT 576 ms.]

![Figure 3. ECG after magnesium 1 g IV with ventricular rate of 51/min, QRS of 134 ms, and QT 614 ms. Taken 2.5 h after arrival.](http://example.com/figure3.png)
In a case series by Marraffa et al., three out of five of the patients had life-threatening cardiac dysrhythmias temporally related to loperamide abuse. Notably, these dysrhythmias were resistant to sodium bicarbonate, magnesium, intravenous lipid emulsion therapy, amiodarone, and cardioversion. Two of these patients required override transvenous pacing and/or isoproterenol. All patients had resolution of conduction abnormalities after cessation of loperamide and two patients had subsequently normal electrophysiology studies.[7] Enakpene et al. described a 25-year-old woman who presented to the ED on multiple occasions with syncope and ventricular dysrhythmias. The patient had a dual chamber implantable cardioverter defibrillator placed on her second hospitalization and it was not until she presented a third time to the ED with unstable polymorphic ventricular tachycardia after failure of her pacemaker to capture that the history of loperamide abuse was obtained. In that case attempts to manage the dysrhythmia with lipid emulsion, bicarbonate, and transcutaneous pacing were unsuccessful. A few months after the third hospitalization the patient re-presented in cardiopulmonary arrest after continued loperamide abuse.[8] Spinner et al. 2015 reported a patient with loperamide abuse who developed cardiac dysrhythmias that were refractory to lidocaine and amiodarone requiring transvenous pacing.[9] In another case report isoproterenol describes successful use of isoproterenol to manage a patient with recurrent torsades de pointe associated with ingestion of high-dose loperamide with cimetidine.[10] The non-sustained ventricular tachycardia observed in our patient resolved spontaneously and did not require intervention. A plan to start isoproterenol with or without transvenous pacing was discussed with the cardiology team, but was never required. Limitations of this case report include the inability to determine causality, the possibility of co-ingestants, and lack of facility to control for confounding factors.

Although previously thought to be devoid of abuse potential, loperamide is quickly becoming a drug of abuse. CNS penetration and resulting opioid effects can be achieved via supra-therapeutic dosing or with co-ingestion of p-glycoprotein inhibitors such as quinine. Given the current epidemic of prescription opioid abuse, toxicity related to loperamide, an inexpensive opioid agonist readily available without a prescription, is occurring more frequently. Further investigation into the mechanism of cardiac toxicity and reporting of adverse events after loperamide overdose to Medwatch are imperative to better understand and address the growing risk of loperamide abuse. It is important for clinicians to be aware of the potentially life-threatening cardiac toxicity related to loperamide abuse in order to provide diagnosis and patient education.

Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

References


Figure 4. Telemetry strip with non-sustained ventricular tachycardia approximately 9 h after presentation. Dysrhythmias lasted seconds and resolved spontaneously without intervention.


