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## Loperamide Trends in Abuse and Misuse Over 13 Years: 2002–2015

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### Abstract

**Study Objective:** With the increasing amount of information available on the Internet describing techniques for using loperamide either for self-treatment of opioid withdrawal syndromes or for recreational use (“legal highs”), the objective was to describe a statewide

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poison control system's experience with loperamide misuse and abuse, with specific interest in cases of cardiotoxicity, and to determine if there has been a recent increase in reported loperamide misuse or abuse cases.

**Design:** Retrospective review.

**Data Source:** Statewide poison control system electronic database.

**Patients:** Two hundred twenty-four adults who presented or were referred to a health care facility between January 1, 2002, and November 10, 2015, for intentional ingestions of loperamide, and whose cases were reported to the poison control system by either physicians or nurses at the bedside.

**Measurements and Main Results:** Between 2002 and 2013, the number of yearly calls to the poison control system regarding loperamide cases ranged from 12–19 (mean 16.4, median 17.5 calls). In 2014, a sharp increase to 41 calls was noted. On completion of the study (November 10, 2015), 27 calls had been recorded. Medical outcomes of loperamide exposure for each patient were classified in accordance with the American Association of Poison Control Center's classification system as minor, moderate, or severe. For those patients with known outcomes, three resulted in death, nine had major effects, 49 had moderate effects, and 36 had minor effects. We identified nine reports of patients who developed cardiotoxicity, with eight of them occurring between 2012 and 2015. A spike in the number of cases of loperamide toxicity reported in 2014 and 2015 coincided with an

abundance of online instructions on how to abuse this drug. Almost all cases of recorded cardiotoxicity occurred over the last 3 years. Cardiotoxicity from loperamide abuse has only recently been recognized as a potential complication during the last few years, so it is likely that earlier cases of cardiotoxicity resulting from loperamide abuse were missed.

**Conclusion:** Our data suggest that loperamide may be increasing in popularity as a drug of abuse and for treatment of opioid withdrawal symptoms. Given the potential for significant toxicity with loperamide exposure, including life-threatening cardiac dysrhythmias, clinicians should consider obtaining a screening electrocardiogram for patients presenting after acute or chronic high-dose ingestions of loperamide. In addition, increased control over the availability of loperamide may be warranted.

Loperamide is a readily available over-the-counter medication used to treat diarrhea. The drug functions pharmacologically as a peripherally acting  $\mu$ -opioid receptor agonist in the gastrointestinal tract.<sup>1</sup> In previous studies, loperamide has been reported to be both safe and effective, with minimal adverse events when used at the recommended therapeutic dosage.<sup>2</sup> The recommended dosage of loperamide is 4 mg orally for acute diarrhea followed by 2 mg after each loose stool, and this dosage regimen appears to be well tolerated in adults<sup>3,4</sup>. Early reports of significant loperamide toxicity after administration of therapeutic doses were described in several infants in Southeast Asia who developed respiratory depression after the use of a loperamide drop formulation for diarrhea.<sup>5</sup> This formulation was removed from the market shortly thereafter; however, today loperamide remains available in multiple over-the-counter preparations worldwide. Since roughly 2008 and rapidly increasing through 2011, descriptions of loperamide misuse began to

appear in various online recreational drug use forums<sup>6,7</sup>. Users described opioid-like highs and treatment of opioid withdrawal symptoms when loperamide was ingested orally in large quantities.<sup>6,7</sup> Recently, there have been several reports linking life-threatening and fatal dysrhythmias with high-dose loperamide.<sup>8-14</sup>

The characteristics surrounding loperamide misuse and abuse are not well described outside of individual case reports. Our goal was to describe a statewide poison control system's experience with loperamide misuse and abuse, with specific interest in cases of cardiotoxicity, and to determine if there has been a recent increase in reported loperamide misuse or abuse cases.

## **Methods**

The California Poison Control Systems (CPCS) maintains an electronic database (Visual Dotlab Enterprise, Madera, CA) for all calls. The CPCS serves a population of 39 million and receives nearly 300,000 calls annually.<sup>15</sup> CPCS data for each call are collected by trained poison center specialists (i.e., Specialists in Poison Information). For each call, the type and route of exposure, as well as standardized codes for signs, symptoms, and treatments, are all recorded.

We performed a search of the CPCS electronic database from January 1, 2002, through November 10, 2015, for all human cases involving the intentional misuse or abuse of loperamide in patients aged 18 years or older who presented to or referred to a health care facility. Patients were excluded if they did not arrive at the health care facility or if their

outcomes were lost to followup. All patients were de-identified prior to review, and this study was deemed exempt by the University of California San Francisco Committee on Human Research.

An electronic data collection spreadsheet was created using Microsoft Excel software (Microsoft Corp., Redmond, WA). Data collected for each case included age, sex, date of loperamide ingestion, loperamide dose ingested, presenting symptoms, coingestions, reason for loperamide ingestion (abuse, misuse, or unknown), electrocardiogram (ECG) results, QRS/QTc-interval measurement, whether the patient was intubated, length of stay, and final outcome. Abuse was defined as recreational use and dependence, misuse was defined as use for nonindicated symptoms or abnormal dosing for indicated uses, and withdrawal was defined as treatment for opioid withdrawal symptoms. Cardiotoxicity was considered present if patient developed any dysrhythmias, significant ventricular ectopy, widened QRS length (>120 msec), or prolonged QTc interval (>500 msec).

Medical outcomes of loperamide exposure were classified in accordance with the American Association of Poison Control Center's classification system as minor, moderate, or severe.<sup>15</sup> Minor effects were defined as development of some signs or symptoms as a result of exposure, but they were minimally bothersome and resolved without residual disability or disfigurement.<sup>15</sup> Moderate effects were defined as signs or symptoms that resulted from exposure, were more pronounced, more prolonged, or more systemic in nature than minor effects but resulted in no residual disability or disfigurement.<sup>15</sup> Major effects were defined

as signs or symptoms resulting from exposure that were life-threatening or resulted in residual disability or disfigurement.<sup>15</sup>

## Results

A total of 265 patients who had intentional misuse or abuse of loperamide were identified. Of these, 34 were excluded due to failure to present to the hospital, two were excluded due to miscoding (incorrect medication documented [e.g., diphenoxylate-atropine or bismuth subsalicylate]), and five were excluded for loss of follow-up data, leaving 224 patients. Their ages ranged from 18–90 years old; median age was 41 years. One hundred three patients (46%) were male, and 121 (54%) were female. Table 1 details patient demographics and reasons for loperamide ingestion (abuse, misuse, suicide, or unknown). There were 36 cases with minor effects, 49 with moderate effects, nine with major effects, and three deaths. The major effects recorded were respiratory depression, dysrhythmias, and central nervous system depression. Loperamide doses ranged from 8–400 mg daily. Coingestants were identified in two of the three fatalities: methadone and ethanol (one patient), and ethanol and diphenhydramine (one patient). Information regarding coingestants was unavailable for the third patient.

During the years 2002-2015, a mean  $\pm$  SD of  $18.9 \pm 6.96$  cases of loperamide toxicity were reported each year. We observed a significant spike in incidence in 2014 and 2015, with 41 cases in 2014 and 27 cases through November 2015. Figure 1 depicts the numbers of cases reported each year.

Sixty-four (28.6%) of the 224 patients were admitted to the hospital. For patients in whom a reason could be identified for loperamide use, eight were using loperamide recreationally, 71 were misusing loperamide (nine of which were using it for treatment of opioid withdrawal symptoms), and 83 were using it in a suicide attempt. Another 62 patients were using excessive doses of loperamide for unclear reasons. No patients used loperamide for self-treatment of opioid withdrawal symptoms prior to 2011.

We identified nine cases of cardiotoxicity, with the majority reported in 2012. ECG results were only reported in 20 (9%) of the 224 patients. ECG abnormalities reported included torsade de pointes, ventricular tachycardia, widened QRS interval, and prolonged QTc interval. The cases in which cardiotoxicity occurred are reported in Table 2. Treatments used for cardiotoxicity included sodium bicarbonate, amiodarone, and naloxone.

## **Discussion**

As reported by Daniulaityte in 2013, methods of misuse of loperamide have been described in online forums as early as 2008.<sup>7</sup> A simple online Web search will reveal several drug abuse forums with instructions on how to abuse loperamide recreationally.<sup>7</sup> Given the ever-expanding amount of information available in the public domain, we sought to determine if a recent increase in loperamide calls to a state poison control system has occurred. Although overall rates of calls regarding intentional abuse and misuse of loperamide remained steady through 2002-2013, we did observe a substantial increase in 2014 and again in 2015. It is unclear if this is a new trend or if more calls are being reported due to the recent identification of the potential dangers of loperamide.

A previous poison control study identified 216 cases of loperamide ingestions between November of 1988 and February of 1993.<sup>16</sup> During this study period, no cases of cardiotoxicity were identified, but several cases of drowsiness and lethargy were noted. This was possibly due to the opioid effects of the drug. Another case report highlighting the central opioid effects of loperamide described a 15-month-old infant who developed respiratory depression, which was reversed by intravenous naloxone.<sup>17</sup> Several fatalities due to paralytic ileus were also identified in infants in Pakistan who were receiving 2-15 drops of loperamide oral solution (2-mg/ml formulation).<sup>3</sup>

The risk of severe cardiotoxicity has only recently been recognized following supratherapeutic dosing of loperamide, and this may explain why ECG results were obtained in only 9% of all patients. It is striking that signs of cardiotoxicity occurred in almost half these patients with all but one occurring after 2012.

The majority of the cases of loperamide cardiotoxicity involved users who reported chronic daily use of high doses. In previously identified cases, success in treating dysrhythmias has been reported with the use of isoproterenol.<sup>9,10,18,19</sup> Other reported treatments included atropine, amiodarone, lidocaine, and sodium bicarbonate.<sup>9,10,12,14,14,18</sup>

Case reports of loperamide toxicity thus far have shown ECGs with widening of the QRS complex, prolongation of the QTc interval, and a Brugada-like pattern, so it remains feasible that high-dose loperamide may interfere with sodium channel conductivity in cardiac



tissue.<sup>6,7,8,12,19,20</sup> Our study identified similar abnormalities including a Brugada-like pattern, torsade de pointes, ventricular tachycardia, prolonged QTc interval, and widened QRS complex.

### Limitations

There were several limitations to our study. The data were collected retrospectively from the poison control center database, which limited the information that could be obtained for each case. ECGs were reported only in a minority of cases.

All data collected by the specialists in poison information were obtained secondhand by reports from either physicians or nurses at the bedside. Additionally, as cardiotoxicity due to loperamide abuse or misuse has been only recently recognized as a potential complication, there may have been several cases in the past that were missed. As we included only cases reported to the poison system in which the patient was evaluated in a health care facility, our results likely do not reflect the overall incidence of loperamide misuse or abuse.

### Conclusion

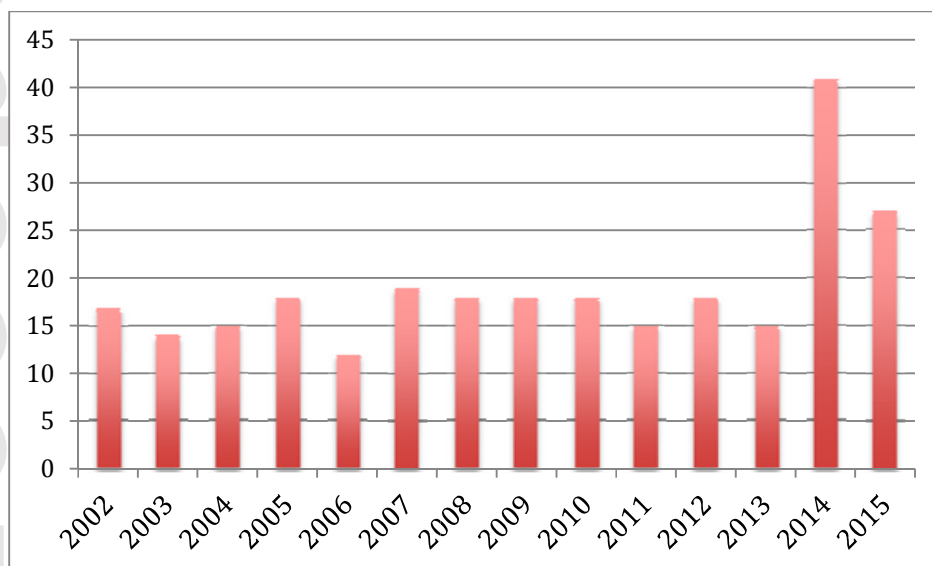
Reports of intentional ingestions of supratherapeutic doses of loperamide appear to be on the rise, particularly over the past 2 years. Given the recent recognition that loperamide toxicity can lead to life-threatening cardiac dysrhythmias, clinicians should be aware of the potential danger of this potential complication. Clinicians should consider obtaining a screening ECG for patients presenting after acute or chronic high-dose ingestions of

loperamide. In addition, increased control over the availability of loperamide may be warranted.

**Table 1. Demographic Characteristics of the 224 Patients and Reasons for Loperamide Ingestion**

Characteristic	Data
<b>Age (yrs)</b>	
<b>Median</b>	41
<b>Mean</b>	45.1
<b>Range</b>	18-90
<b>Sex, no. (%)</b>	
<b>Male</b>	103 (46)
<b>Female</b>	121 (54)
<b>Reason for ingestion, no. (%)</b>	
<b>Abuse</b>	8 (3.6)
<b>Misuse</b>	71 (31.7)
<b>Suicide</b>	83 (37.1)
<b>Unclear or unknown</b>	62 (27.7)

**Figure 1.** Number of cases of reported loperamide misuse or abuse by year (through November 2015) in a statewide poison control system.



**Table 2.** Summary of Cases of Loperamide Abuse or Misuse Involving Cardiotoxicity

	Patient Demographics	Date	Ingestion size	Reason for ingestion	Cardiac Abnormalities	Coingestions	Treatments Rendered	Paient Outcome
Case #1	45y.o. F	9/12/06	Unknown	Unknown	Ventricular Tachycardia, Torsades de Pointes, Prolonged QTc	Methadone	Atropine, Sodium Bicarbonate, Amiodarone	Death
Case #2	31y.o. M	9/30/12	200mg daily	Self treatment of opiate withdrawals	Prolonged QTc of 592, Bigeminy	Cimetidine, Dextromethorphan	Narcan	6 Day ICU stay. Discharged home without complication
Case #3	29y.o. M	10/15/14	300mg daily	Self treatment of opiate withdrawals	Wide QRS of 152ms, Prolonged QTc of 683ms	Dextromethorphan and chlorpheniramine	Sodium Bicarbonate	3 Day ICU stay. Discharged home without complication
Case #4	83y.o. M	4/19/15	400mg daily	Attempted weight gain	QRS 114, QTc 493, Brugada like pattern	None		2 day hospital stay and discharge without complication
Case #5	24y.o. F	4/20/15	400mg daily	Self treatment of opiate withdrawals	ST-T changes	None		2 day hospital stay and discharge without complication
Case #6	41y.o. F	4/24/15	240mg daily	Self treatment of opiate withdrawals	Prolonged QTc of 523, 1st degree heart block, syncope	Unknown		2 day hospital stay and discharge without complication
Case #7	23y.o. M	6/5/15	Unknown	Unknown	Ventricular Tachycardia	Unknown	Amiodarone	Lost to follow up
Case #8	22y.o. M	6/6/15	400mg	Abuse	Arrythmia, unspecified	Unknown		Lost to follow up
Case #9	24y.o. M	9/17/15	400mg daily	Self treatment of opiate withdrawals	Prolonged Qtc, Ventricular Tachycardia	Cimetidine	Amiodarone	3 Day ICU stay. Discharged home without complication

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