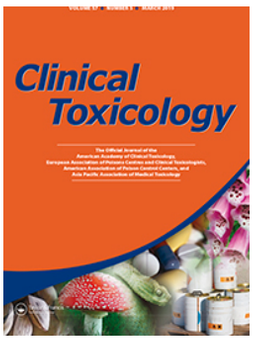

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CLINICAL RESEARCH

Loperamide misuse to avoid opioid withdrawal and to achieve a euphoric effect: high doses and high risk

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ABSTRACT

Introduction: Loperamide is a readily accessible nonprescription medication that is increasingly being used surreptitiously as an opioid substitute to alleviate the symptoms of acute opioid withdrawal. The objective of this study was to determine the clinical characteristics of patients with loperamide misuse and toxicity.

Methods: The ToxIC registry, a nationwide, prospectively collected cohort of patients evaluated by medical toxicologists was searched from November 2011–December 2016 for patients with loperamide exposure. Each record was reviewed to determine the circumstances, dose, clinical presentations, treatment, and outcomes associated with loperamide use.

Results: Twenty-six cases were identified, and both the absolute number and relative proportion of overall cases in the ToxIC registry increased annually. The median age was 27 and 54% were male. Of cases with known intent ($n = 18$), 12(67%) were misuse/abuse, 3(17%) were self-harm/suicide, and 3(17%) were pediatric exploratory ingestions. Circumstances for misuse included taking higher doses than labeled ($n = 7$), avoiding withdrawal ($n = 6$), and gaining a pleasurable sensation ($n = 4$). The dose was reported in nine cases and ranged from 4 mg to 400 mg. In patients seeking to avoid withdrawal doses were 160–400 mg/day; the most common reported dose was 200 mg. Reported ECG abnormalities included 10 cases of prolonged QTc (>500 ms), which consisted of misuse/abuse ($n = 6$) and self-harm ($n = 1$) exposures; six prolonged QRS (>120 ms); two first degree AV block; seven ventricular dysrhythmias, five of which were single-agent exposures. All but one ECG demonstrated prolonged QTc with a range of 566–749 ms. All patients with dysrhythmias in which dose were reported ingested ≥200 mg.

Conclusions: The majority of patients had loperamide toxicity due to misuse/abuse, in-line with national trends. In patients avoiding withdrawal, doses >100 mg were observed. When taken in large doses (>200 mg), loperamide may cause significant cardiovascular effects, including QTc-prolongation and ventricular dysrhythmias.

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Cardiac arrhythmia; loperamide; substance abuse

1. Introduction

The U.S opioid epidemic continues to worsen, with reported drug overdose deaths nearly quadrupling during 1999 to 2015. According to the Centers for Disease Control and Prevention (CDC), an increase of 5,349 (11.4%) in drug overdose deaths and opioid death rates (15.6%) occurred from 2014 to 2015 [1]. These significant increases were comprised of deaths due to synthetic opioids other than methadone (72.2%), which include heroin, illicitly manufactured fentanyl and fentanyl analogs, and prescription opioids. At the same time, the abuse of related opioid compounds, such as loperamide and dextromethorphan, appears to be on the rise [2].

Loperamide is an antidiarrheal synthetic opioid that has been widely available to the U.S public after being approved for nonprescription use in 1988 [3]. A phenylpiperidine with a chemical structure similar to diphenoxylate, haloperidol, and meperidine, it has minimal analgesic activity when used at therapeutic doses. In the U.S., nonprescription loperamide preparations are sold as 2 mg tablets, caplets, and capsules, a 1 mg/5 ml oral solution, and a 1 mg/7.5 ml oral suspension. Loperamide acts as a peripheral μ-opioid agonist in the myenteric plexus of the large intestine, inhibiting secretion and peristaltic activity, thereby increasing gastrointestinal transit time. Central nervous system (CNS) effects are minimal at standard therapeutic doses for three reasons: (1) poor oral bioavailability (0.3%) due to limited gastrointestinal absorption, (2) rapid first pass hepatic metabolism by cytochrome P450 3A4 and 2C8), and (3) p-glycoprotein-mediated efflux out of the CNS. As a result, adverse effects are relatively rare, typically minor, and are self-limiting in nature [4].

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Nonetheless, reports of loperamide misuse are on the rise. Since 2010, there has been an increasing prevalence of discussions on internet forums related to loperamide, in particular regarding its euphoric effects and ability to self-treat opioid withdrawal [5]. The majority of reports mention using extremely high doses of loperamide, averaging 70 mg per day, and ranging from 100 mg to 200 mg per day, equivalent to 50-100 2 mg pills. The 2015 report of the American Association of Poison Control Centers notes 1232 case mentions for loperamide, including 916 single drug exposures and two deaths [6]. There was a 91% increase in reported exposures from 2010 to 2015, half of which were single-agent loperamide use [3]. When ingested at supratherapeutic doses, loperamide may elicit an opioid toxidrome. Recently, multiple cases of ventricular arrhythmias associated with prolonged QRS and QTc intervals have been linked to loperamide misuse when taken at higher than recommended doses [2, 3, 7–21].

There have been numerous published case series and review articles about emerging misuse of loperamide, particularly in high doses inducing life-threatening cardiotoxicity [2, 3, 7–9, 11–13, 18, 22–25]. Our study represents a sizable cohort describing the clinical characteristics of patients with loperamide exposure. By utilizing the unique capabilities of the national Toxicology Investigators Consortium (ToxIC) Case Registry we were able to provide detailed clinical descriptions. Demographic characteristics, management, and medical outcomes reported by medical toxicologists treating these patients at the bedside were prospectively collected in cases reported to the ToxIC case registry.

2. Material and methods

2.1. Study design and setting

This is a multicenter cohort study of patients presenting to medical care after a history of loperamide exposure. In 2010, the American College of Medical Toxicology established the ToxIC Registry as a toxicology surveillance and research tool. We identified cases of loperamide exposure in the ToxIC Registry, a prospective registry of patients seen by medical toxicologists at 50 sites in the USA. The ToxIC Registry contains data from all clinical cases cared for in-person by medical toxicologists at participating sites, which is the primary qualification for a case to enter the registry. To enter patients into the ToxIC Registry, participating medical toxicologists use an online interface to upload information including substance involved, demographics, encounter circumstances, toxidrome, signs and symptoms, treatment, and outcomes.

Loperamide cases were identified in the ToxIC Registry by searching the "agent" section for cases recorded between the inception of the registry, January 5, 2010, through December 5, 2016. Cases coded as loperamide exposure were extracted into a spreadsheet using predefined variables noted in Tables 1 and 2. The diagnosis of loperamide intoxication was made based on the patient history and clinical impression of the consulting toxicologist. Both asymptomatic exposures and cases of toxicity were included in the study. Confirmatory lab testing was not performed; however, self-report and collateral confirmation is validated and reliable techniques in substance abuse research. Only U.S. sites were included in this study since no cases were reported at international ToxIC sites. Research using the prospectively collected, patient de-identified data within the ToxIC Registry has been determined to be exempt from Institutional Review Boards review as defined under Federal regulation 45 CFR 46.102(f) by written determination by the Western Institutional Review Board. Nevertheless, all participating sites do so pursuant to permission from their local Institutional Review Boards.

Table 1. Definitions of severe vital sign abnormalities.

Vital sign	Definition of abnormality
Hypertension	Systolic blood pressure >200 mmHg and/or diastolic blood pressure >120 mmHg
Hypotension	Systolic blood pressure <80 mmHg
Tachycardia	Heart rate >140 beats per minute
Bradycardia	Heart rate <50 beats per minute
Bradypnea	Respiratory rate <10 breaths/min
Hyperthermia	Temperature >105 degrees Fahrenheit

Table 2. Definitions of clinical characteristics.

Cardiovascular	
Prolonged QTc	≥500 ms
Prolonged QRS	≥120 ms
Metabolic	
Acidosis	pH <7.2
Elevated anion gap	>20
Elevated osmolality gap	>20
Hypoglycemia	Serum glucose <50 mg/dL
Acute kidney injury	Serum creatinine >2.0 mg/dL
Rhabdomyolysis	Serum creatinine phosphokinase >1000 units/L
Hematology	
Hemolysis	Hemoglobin <10 g/dL
Leukocytosis	> 20,000 × 10^9 cells/L

The definitions of clinical characteristics in the ToxIC registry are shown in Tables 1 and 2. Of note, the collection of QTc interval as an exact value did not begin in ToxIC until March 1, 2015.

2.2. Analysis

Descriptive statistics were used to characterize the patient demographics, clinical features, and treatment characteristics. Missing variable completion was reflected by reporting both the numerator and the denominator of the reported variables. Data were analyzed for epidemiologic and temporal patterns, and demographic, clinical, and exposure attributes were tabulated. Although cases were not restricted to single-agent exposures (i.e., loperamide exposure only), medical outcomes, and therapies provided were assessed between single and polysubstance exposures.

3. Results

3.1. Patients

Twenty-six cases determined to be loperamide toxicity were identified. Demographic data of patients are shown in Table 3. The absolute number and relative proportion of

overall cases in the ToxIC registry increased progressively over time (Figure 1). Furthermore, the number of single-agent loperamide only exposures increased in parallel. Of the 18 cases with known intent, 12 (67%) were for misuse/abuse, 3 (17%) were for attempted self-harm, and 3 (17%) were pediatric exploratory ingestions. Specific circumstances for misuse/abuse were eight cases taking higher doses than labeled, six cases attempting to avoid opioid withdrawal, and four cases in an attempt to gain a pleasurable sensation (multiple response options were possible for a single patient). See Table 4 for list of loperamide co-ingestions. The dose was reported in nine cases and ranged from 4 mg (pediatric exploratory ingestion) to 400 mg. In patients seeking to avoid withdrawal doses were 160-400 mg/day; the most common reported dose was 200 mg ($n = 4$).

3.2. Clinical presentations

Twenty (76.9%) patients were reported to have signs or symptoms associated with use of loperamide as determined by the treating medical toxicologist. The remaining six patients were asymptomatic. Clinical findings and major vital sign abnormalities are shown in Table 5.

Prolonged QTc was reported in 10 (38.5%) out of 26 patients, 5 (50%) of whom had ventricular dysrhythmias. Of these patients with prolonged QTc ($n = 10$), 9 were due to misuse/abuse, including one pediatric patient (age 17 years), and one was due to self-harm. Of those with ventricular dysrhythmias, 5/6 had single-agent exposures. All but one had prolonged QTc with a range of 566-749 ms; all patients with ventricular dysrhythmias in which dose was reported ingested 200mg or greater. The highest two reported QTc values (749 ms and 725 ms) co-ingested cimetidine, a known p-glycoprotein and CYP 3A4 inhibitor. Prolonged QRS was reported in 6 (23.1%) patients. Two patients had 1st degree AV block. One patient (3.8%) had myocardial injury and infarction. There were no reported deaths.

3.3. Treatments

Seventeen (65%) patients required specific toxicological treatment for toxicity. The most common pharmacological interventions were the administration of an opioid antagonist

Table 3. Demographic characteristics of patients captured by the ToxIC registry with exposure to loperamide.

Demographic variable n = number in which data was captured	n (%), unless otherwise specified
Age range, $n = 26$	
<2	1 (3.85%)
2–6	3 (11.5%)
13–18	3 (11.5%)
19–65	17 (65.4%)
66–89	2 (7.69%)
Specific age captured, $n = 23$	Median 27 (range 2–89, IQR 17.5, 36)
Gender, $n = 26$	
Male	14 (53.9%)
Female	12 (46.2%)
Location of consult: initial, $n = 26$	
ED	6 (23.1%)
ED and hospital floor	1 (3.85%)
ED and ICU	2 (7.69%)
Hospital floor	3 (11.5%)
ICU	10 (38.5%)
Unknown	4 (15.4%)

Table 4. Frequency of co-ingestants with loperamide exposures.

Frequency of co-ingestants	n (%)
Single exposure (loperamide only)	19 (73)
Co-Ingestions	21 (80)
Antihistamines	3 (12)
Dextromethorphan	2 (7)
Cimetidine	2 (7)
Metoclopramide	2 (7)
Vitamins	2 (7)
Aspirin	1 (4)
Amlodipine	1 (4)
Diazepam	1 (4)
Nystatin	1 (4)
Naproxen	1 (4)
Methylphenidate	1 (4)
Hydrocarbon	1 (4)
Levetiracetam	1 (4)
Risperidone	1 (4)
Phenylephrine	1 (4)

Multiple co-ingestants may be present in one patient.

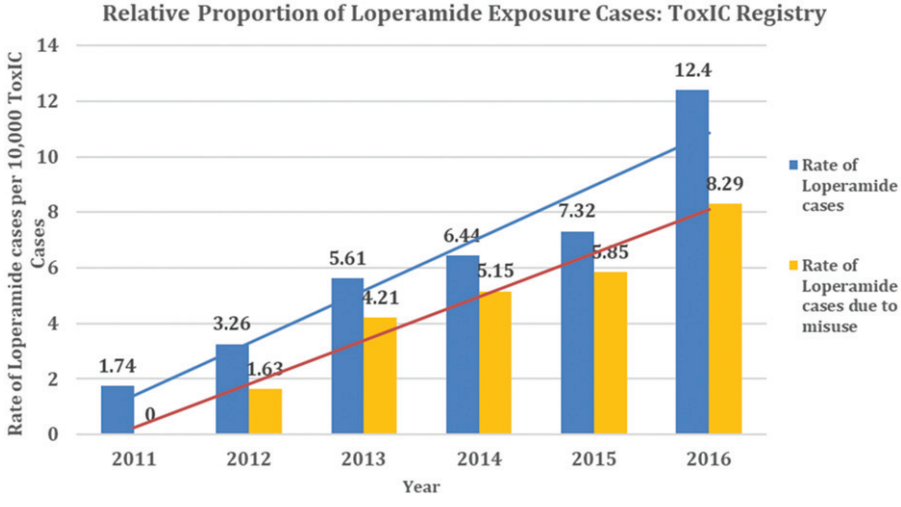

Figure 1. Relative proportion of loperamide exposure cases: ToxIC Registry.

Table 5. Clinical presentations: major vital sign abnormalities and signs and symptoms reported from loperamide intoxication.

Major vital sign abnormalities	
Bradycardia	4 (15.4%)
Hypotension	3 (11.5%)
Bradypnea	4 (15.4%)
Tachycardia	2 (7.7%)
Signs and symptoms	
Neurological	
Coma & CNS depression	11 (42.3%)
Seizure	1 (3.8%)
Hyperreflexia, myoclonus, clonus, & tremor	1 (3.8%)
Delirium & toxic psychosis	1 (3.8%)
Pulmonary	
Respiratory depression	5 (15.4%)
Aspiration pneumonitis	2 (7.7%)
Renal	
Rhabdomyolysis	3 (11.5%)
Acute kidney injury	3 (11.5%)
Metabolic	
Elevated anion gap metabolic acidosis	2 (7. 7%)
Hypoglycemia	1 (3.8%)
Hematology	
Hemolysis	1 (3.8%)
Significant leukocytosis	1 (3.8%)

(n =6, 23%) benzodiazepines (n =3, 11%), and treatment for dysrhythmia or conduction disturbances, including sodium bicarbonate (n =4, 15%), isoproterenol (n =2, 8%), and amiodarone (n =1, 4%). Four patients (15%) were intubated for ventilatory management, three of whom had ventricular dysrhythmias. Two patients (8%) had a pacemaker intervention, both experiencing ventricular dysrhythmias. One patient (4%) with ventricular dysrhythmia required cardiopulmonary resuscitation, intubation with mechanical ventilation, vasopressors, and pacemaker intervention and survived.

4. Discussion

This prospectively collected cohort from the ToxIC registry illustrates the growing problem of loperamide misuse and abuse in the midst of the opioid epidemic. Loperamide is emerging as an inexpensive over-the-counter alternative for ameliorating opioid withdrawal. Patients reporting misuse or abuse were found to be predominantly young Caucasians with a relatively even gender distribution. This is consistent with epidemiologic studies on prescription opioid abusers [3, 6, 26]. Patients with prolonged QTc consisted exclusively of those using loperamide for misuse/abuse or attempted self-harm. The primary reason for misuse was to relieve the effects of opioid withdrawal and to gain a pleasurable sensation by taking a higher dose than labeled. This is similar to the data in the review by Wu et al. reporting cardiotoxicity in dosages ranging from 100 to 800 mg/day [24]. Of note, the small volume pediatric exploratory ingestions in this case series did not develop toxicity.

The mechanism of loperamide's cardiotoxicity is currently unknown, but *in vitro* studies suggest a high-affinity inhibition of cardiac sodium channels. This slows cardiac depolarization and causes QRS prolongation. QTc interval prolongation is likely due to inhibition of the delayed rectifier potassium current (Ikr) [9]. This current is responsible for cardiac repolarization and terminates the action potential; inhibition leads to delayed repolarization, which predisposes to early after-depolarization, heterogeneous myocardial repolarization, and Torsades de Pointes (TdP) [14]. Published case reports and studies in literature are in agreement with this mechanism [10–14], and there is some evidence to suggest cardiotoxicity is due to the metabolite, desmethylloperamide, and not the parent compound [23, 27].

The most common clinical abnormality observed in this study included coma and CNS depression. When loperamide is taken in labeled dosages (maximum daily dose 16 mg), patients do not exhibit typical opioid-like effects such as respiratory depression or euphoria. However, there have been published case reports describing CNS depression, convulsions, and coma after therapeutic oral dosing in infants and neonates rescued by naloxone [25, 27–29]. Furthermore, Sadeque et al. (2000) demonstrated increased CNS effects when loperamide was taken at typical daily dosages with quinidine, a p-glycoprotein inhibitor. This suggests that when taken in supratherapeutic doses or with p-glycoprotein inhibitors, loperamide can overcome p-glycoprotein efflux at the blood-brain barrier and cause opioid-like CNS effects [8].

Cardiotoxicity, also a common finding in this cohort, included bradycardia, tachycardia, QTc-prolongation, and QRS prolongation and ventricular dysrhythmias. One patient required cardiopulmonary resuscitation, intubation, ventilation, vasopressors, and pacemaker intervention. Patients experiencing ventricular dysrhythmias had ingestions of 200 mg or greater; the same was true for patients with QTc-prolongation. These findings are similar to previously published cases of patients ingesting excessive doses of loperamide [17, 20, 21]. The U.S Food and Drug Administration Adverse Event Reporting System database contains 48 cases of loperamide cardiotoxicity, with the majority occurring in the setting of drug abuse for the purpose of producing euphoric effects or preventing opioid withdrawal [7]. Of patients abusing loperamide in that database, the median daily dosage was 250 mg, ranging from 70 mg to 1600 mg. Frequently reported cardiac events included cardiac arrest, QT-interval prolongation, ventricular tachycardia, and TdP.

Since first being described in 2005 on web-based discussion forums for its misuse of euphoric effect and self-treatment of opioid withdrawal [5], there has been a growing number of reported loperamide toxicity cases to poison control centers [2, 3, 6, 18, 19, 30]. Our study, based on bedside reports from medical toxicologists caring for the patient, found an increase in both the absolute and relative proportion of loperamide misuse/abuse since 2011. This is consistent with epidemiologic data showing an increase in the misuse of loperamide from 2010 to 2015 [2, 3, 6, 18, 19, 30]. Data from U.S poison control centers indicate that since 2006, and particularly 2010, calls have increased for intentional loperamide exposures [6, 30]. During 2010 to 2011, forums experienced a 10-fold increase in posts of users discussing loperamide as a remedy for opioid withdrawal symptoms (70%) and for producing a euphoric effect (25%) [5].

Furthermore, these forums have discussed methods of increasing CNS penetration and the resulting opioid effects via supratherapeutic dosing or with co-ingestion of

p-glycoprotein inhibitors. There are several published reports of patients exploiting the CYP3A inhibition and p-glycoprotein inhibitory effect of cimetidine and nystatin, respectively [22, 31–34], presumably for enhancing the effect of loperamide [18].

Although loperamide was believed to be of low abuse potential [16], since its move to nonprescription status in 1988, loperamide has evolved from being an over-the-counter antidiarrheal to being the "poor man's methadone", used for self-relieving the effects of opioid withdrawal and its euphoric effects. This behavior may be worsened by the absence of available methadone or buprenorphine treatment programs, although that is not known in this study. Possible ways of restricting loperamide misuse may include limiting the daily/monthly amount any individual could purchase, requiring retailers to keep personal information about customers, and requiring photo identification for purchase, placing medication behind the counter; similar to the Drug Enforcement Administration's regulation of pseudoephedrine as mandated by the Combat Methamphetamine Epidemic Act of 2005 [35]. To prevent the incidence of large-dose pediatric exploratory ingestions, loperamide can be placed in unit-dose packaging, similar to iron packaging regulation [36]. Furthermore, the United States Food and Drug Administration is continuing to evaluate the safety issue of loperamide to determine if additional regulatory actions are needed.

4.1. Limitations

This study only characterizes patients seen at the bedside by medical toxicologists and thus likely overestimates the severity of illness in users due to typical consulting patterns for sicker patients. Therefore, ToxIC registry cases likely are not representative of the majority of toxicological exposures that were not hospitalized or had minimal signs or symptoms of toxicity. The data in the ToxIC registry are limited by voluntary participation by medical toxicologists, thus it is possible that clinical data were underreported by providers or reported in error. Consulting medical toxicologists generally provide treatment recommendations, but in some settings, treatment decisions are the responsibility of the primary physician team caring for the patient. This may have led to treatment practices not recommended by the medical toxicologist. The lack of age-adjusted vital signs in the ToxIC registry may result in misclassification of pediatric cases. The lack of blinding of the authors to the study hypothesis may produce information bias. In addition, the electrocardiograms were not reviewed by the authors, and neither unadjusted QT nor the method of correction to QTc was available for analysis. Finally, these exposures were not confirmed in biologic samples in the vast majority of cases and the report of exposure is taken directly from patient and/or provider report. While lack of confirmatory testing is a limitation, there is substantial support for the validity and reliability of self-report data in substance abuse research.

5. Conclusion

In summary, this study found that the majority of cases of loperamide toxicity were due to misuse and abuse, with the intent to self-treat opioid withdrawal and achieve euphoric effects. Excessive doses were frequently observed, in particular with patients experiencing cardiotoxicity. Co-ingestion of drugs to achieve pharmacokinetic manipulation was also repeatedly described. This report adds to the growing body of literature describing high-dose loperamide misuse and its association with life-threatening toxicity.

Geolocation information

New Jersey Poison Control Center, 40.740663°N, 74.191464°W.

Disclosure statement

No potential conflict of interest was reported by the authors. The authors have no relevant financial relationships to disclose. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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