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RESEARCH

Loperamide misuse and abuse

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ABSTRACT

Objective: The epidemic of opioid prescription deaths in recent years resulted in the recent rescheduling of hydrocodone-containing products to restrict access to them. Opioid users have recognized that loperamide can ameliorate withdrawal symptoms and also produce euphoria in very high doses. This article discusses the potential for loperamide misuse and abuse and examines trends in the increasing number of published cases of loperamide toxicity.
Design: PubMed was used to search MEDLINE for case reports of loperamide abuse.
Setting: United States.
Main outcome measures: Numbers of cases of loperamide misuse, characteristics of patients, reported toxicities.
Results: From 1985 to 2016, 54 case reports of loperamide toxicity were published, with 21 cases between 1985 and 2013 and 33 cases between 2014 and 2016. In addition, 179 cases of intentional loperamide misuse were reported to the National Poison Database System between 2008 and 2016, with more than half reported after January 1, 2014.
Conclusion: Loperamide misuse and abuse is increasing in the United States, and pharmacists are encouraged to monitor and restrict their sales.

Introduction

Opioid misuse has become a growing public concern worldwide. According to the Centers for Disease Control and Prevention, more people died from drug overdose in 2014 than in any year on record, with the majority of these deaths involving opioids.[1] Prescription opioid analgesics appear to be one of the driving forces behind this epidemic, as both sales and deaths associated with prescription opioids have quadrupled since 1999.[1] In 2010, the U.S. Food and Drug Administration (FDA) approved tamper-resistant oxycodone, designed to discourage misuse of the medication.[2] In 2014, the Drug Enforcement Agency rescheduled hydrocodone-containing combination products from Schedule III of the Controlled Substance Act to the more tightly regulated Schedule II in an effort to minimize abuse and misuse potential.[3] As prescription opioids become less accessible, the use of nonprescription preparations, such as loperamide and dextromethorphan, may be on the rise.[4-6]

Loperamide is a commonly used antidiarrheal sold in the United States as a generic or under the trade name Imodium®. It is available with or without a prescription in tablet, capsule, and liquid forms at a recommended dose not exceeding 8 mg/day (nonprescription) or 16 mg/day (prescription). Loperamide is an intestinal μ-opioid receptor agonist thought to have little misuse potential[7]; however, published reports of misuse and overdose have increased in recent years. There have been growing discussions on Internet forums about using high doses of loperamide to alleviate symptoms of opioid withdrawal and to achieve feelings of euphoria.[8-11] The 2014 Report of the American Association of Poison Control Centers notes 1230 case mentions for loperamide, including 887 single exposures and 2 deaths.[12] More recently, multiple cases of cardiac dysrhythmias and prolongation of the QRS and QTc intervals have been linked to loperamide misuse.[13] An analysis of the National Poison Database System identified 179 cases of loperamide misuse from January 1, 2008, to March 31, 2016 (Figure 1).[14] In June 2016, the FDA issued a warning about serious heart problems associated with high doses of loperamide. The FDA urges patients to follow package instructions when using loperamide and health care professionals to consider loperamide as a possible cause of cardiac events.[15]

Objective

This article discusses the potential for loperamide misuse and examines trends in the increasing number of published cases of loperamide toxicity.

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Key Points

Background:

- Loperamide is thought to have very low misuse potential.
- However, it has been misused to prevent opioid withdrawal symptoms or to produce euphoria.

Findings:

- Loperamide misuse is increasing, particularly since 2014.
- Deaths with loperamide misuse implicated are increasing.

Methods

A literature search of PubMed was conducted using the following search terms: "loperamide AND abuse," "loperamide AND dependence," "loperamide AND overdose," and "opioid-related disorders [MeSH] AND loperamide." Only articles in English were included. Reference lists from retrieved articles were examined for additional reports. The authors selected the articles relevant to this review.

Loperamide pharmacology and pharmacokinetics

Loperamide is a phenylpiperidine opioid derivative structurally related to diphenoxylate and haloperidol; it is used in the treatment of acute and chronic diarrhea.[7] The pharmacologic effect is achieved predominantly by binding to opioid receptors in the mesenteric plexi of the enteric wall, inhibiting the release of acetylcholine and prostaglandins and thereby reducing peristalsis and increasing intestinal transit time.[16] Loperamide is also thought to antagonize calcium channels, which may also result in reduced gastrointestinal motility.[17,18]

Plasma concentrations of loperamide remain below 2 ng/mL following ingestion of a 2-mg capsule.[16] Protein binding is approximately 95%. The half-life is approximately 11 hours. It is metabolized through N-demethylation by the cytochrome system. Loperamide and its metabolites are primarily excreted via the feces. Oral bioavailability is low, and penetration through the blood-brain barrier is minimal at recommended doses.[19]

Loperamide was initially believed to have a low abuse and misuse potential because of its poor oral bioavailability, extensive first-pass metabolism, inability for direct penetration through the blood-brain barrier in the central nervous system, and the effect of the P-glycoprotein (P-gp) efflux transporter.[13,17,20] Loperamide undergoes first-pass metabolism by cytochrome P450 3A4 (CYP3A4) and CYP2C8 in the liver leading to inactive metabolites; the extent of first-pass metabolism reduces the ability to achieve dangerous drug concentrations systemically when taken at therapeutic doses.[17] In addition, the P-gp efflux transporter in the blood-brain barrier is responsible for actively pumping out loperamide that reaches the central nervous system resulting in minimal loperamide concentration levels in the brain.[21]

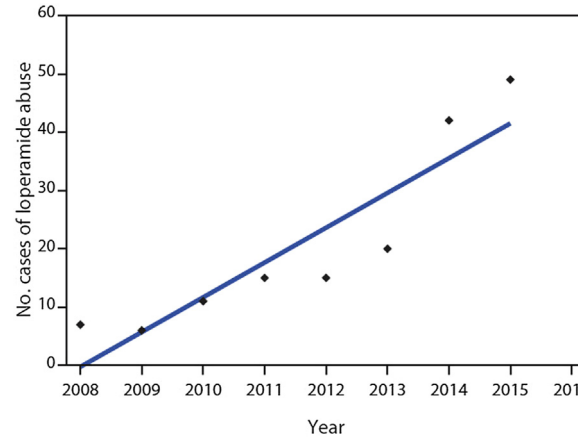


Figure 1. Number of reported cases of intentional loperamide misuse, by year—National Poison Database System, January 1, 2008-March 31, 2016. Reproduced with permission from Eggleston et al.[14]

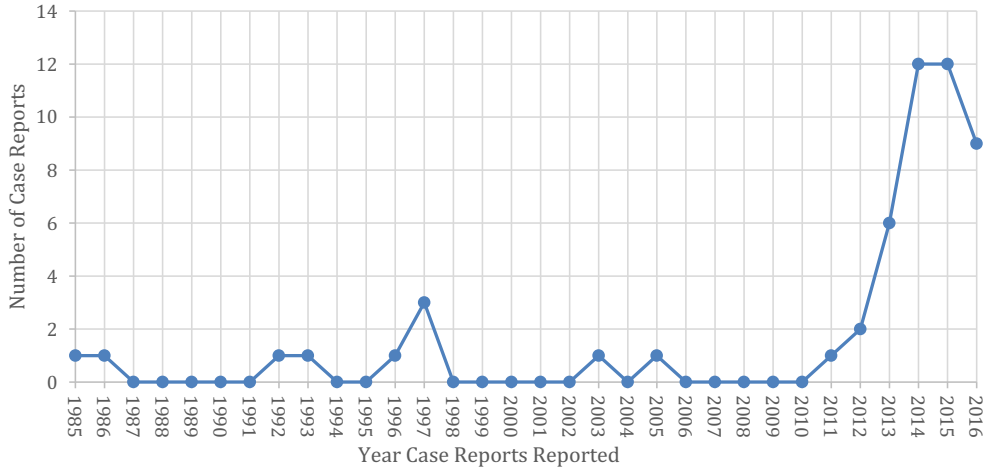
Recent evidence suggests that loperamide possesses centrally active opioid agonist properties in the absence of P-gp activity.[21] This was demonstrated in a rat model when P-gp modulators were given before loperamide dosing, resulting in increased levels of loperamide in the brain.[22]

Although loperamide predominantly acts peripherally, taking sufficiently high doses or taking concomitant medications that inhibit P-gp, CYP3A4, or CYP2C8 can result in toxic serum levels and central nervous system effects.[17,23] The most well-documented drug interaction with loperamide is the coadministration of a P-gp inhibitor, which has been shown to increase the serum loperamide concentration level by up to 3-fold.[16] Examples of drugs that can lead to P-gp inhibition are corticosteroids, quinidine, methadone, ketoconazole, protease inhibitors, antineoplastic drugs, verapamil, and loperamide itself.[17] Because loperamide is metabolized by CYP3A4 and CYP2C8, any inhibitors of these enzymes can increase loperamide serum concentrations. Users have described combining loperamide with agents such as cimetidine and grapefruit juice (both CYP3A4 inhibitors) to reduce opioid withdrawal symptoms.[10]

Common adverse effects when taking therapeutic doses of loperamide can include nausea, constipation, drowsiness, and headache.[13] However, if loperamide overdose occurs or the patient is taking a medication that inhibits the P-gp pump, the patient may experience central nervous system toxicities such as miosis, central nervous system depression, and respiratory depression.[13,24,25] Loperamide misuse is also linked to life-threatening cardiac arrhythmias, including QTc prolongation, which may be connected to its blockade of calcium and potassium channels.[17,19] At large doses, piperidines can block sodium channels similar to lidocaine.[19]

Results

From 1985 to 2016, 54 case reports were published regarding loperamide toxicity, with 21 cases published between 1985 and 2013 and 33 cases published between 2014 and 2016 (Figure 2). This includes 19 cases of loperamide-related deaths reported by the North Carolina Office of the



*The exact year was not documented for two of the case reports published in 1997. A range was given for their occurrence between 1988 and 1991.

Figure 2. Number of case reports reported per calendar year.[13,17-19,23,27-40]

Chief Medical Examiner (NC OCME) between 2012 and 2016.[26] The average number of case reports published per year increased by more than 10-fold in 2014 with an average of less than one case per year between 1985 and 2013 in comparison to 11 cases per year between 2014 and 2016.[13,17-19,23,26-48]

Gender and age

Of all the loperamide-related case reports, males have accounted for the majority, making up 35 of the 54 cases reported from 1985 to 2016. Males had more reported loperamide toxicity cases than females did during 1985-2013 and 2014-2016.

The 25-34-year-old age group accounts for most reports of toxicity, representing 44% of all cases. The prevalence of toxicity in this age group had the greatest increase over time. During 1985-2013, this group represented only 33% of all cases but rose to 52% during 2014-2016.

Comorbid conditions

Among the 54 loperamide case reports, the following comorbid conditions were reported: 27 reported substance use disorder, 6 reported gastrointestinal disorders, 12 reported psychological disorders, 3 reported no significant medical history, 5 reported other medical history, and 10 had no history documented. Twenty-two of the 27 cases reporting substance use disorder occurred between 2014 and 2016.

Table 1
Reported reasons for loperamide misuse[13,17-19,23,27-40]

Rationale for loperamide overdose	1985-2013 (n = 21)	2014-2016 (n = 33)	1985-2016 (n = 54)
Antidiarrheal	10	3	13
Opioid alternative	0	18	18
Suicide attempt and familial conflict	3	0	3
Not reported	8	12	20

Reported rationale for loperamide overdose

Table 1 lists the reported reasons for using loperamide in the case reports published in their respected period. During the years between 1985 and 2013, the main reason reported for loperamide overdose was for diarrhea relief. During the years between 2014 and 2016, there is a noticeable increase in the use of loperamide as an opioid alternative.

Concomitant medications

Among the 54 loperamide-related case reports involving misuse or abuse during 1985-2016, 18 of the patients were not taking any concomitant medications. Sixteen of the cases

Table 2
Loperamide combined with other drugs reported in published case reports during 1985-2013 and 2014-2016[13,17-19,23,27-40]

Loperamide drug combinations	No. case reports, 1985-2013 (n = 21)	No. case reports, 2014-2016 (n = 33)
Loperamide only	9	9
Loperamide in combination with other medications	12	24
OTC medications	5	10
Opioid derivatives	3	5
Other pain relievers	3	6
Benzodiazepines	3	6
Antidepressants	7	7
Antipsychotics	2	1
Loperamide in combination with alcohol and other medications	0	2
Loperamide in combination with alcohol only	0	0
Loperamide in combination with marijuana	0	1
Loperamide in combination with medications that cause QT prolongation	7	11

Table 3
Reported toxicities categorized by organ system[13,17-19,23,27-40]

Organ system	1985-2013 (n = 21)	2014-2016 (n = 33)	Total, 1985-2016 (n = 54)
Gastrointestinal[a]	6	1	7
Cardiovascular[b]	4	15	19
Respiratory[c]	2	2	4
Neurological[d]	4	5	9
Death	10	17	27

[a] Report of epigastric pain, elevated pancreatic enzymes, severe constipation, enlarged bladder, pancreatitis, peritoneal irritation, or appendicitis. Note that patients reported multiple toxicities and percentages do not equal 100%.
[b] Report of syncope, chest pain, cardiac arrhythmia, cardiomegaly, tachycardia, or hypotension.
[c] Report of pulmonary edema, shortness of breath, and increased respiratory rate.
[d] Report of seizures, somnolence, weakness, slurred speech, withdrawal symptoms, delirium, severe motor retardation, loss of consciousness, dizziness, and cerebral edema.

involved loperamide combined with only 1 drug, 6 of the cases reported loperamide in combination with 2 drugs, and 14 of the cases involved loperamide combined with 3 or more drugs.

Table 2 lists medications taken concomitantly with loperamide in the case reports. In general, the concomitant medications did not differ significantly in cases published before and after 2014. However, in many of the case reports after 2014, patients used over-the-counter antihistamines to reduce opioid-induced pruritus, and over-the-counter cimetidine to enhance the effect of loperamide.

Although many of these cases involved multiple medications, loperamide was considered the primary or additive cause of toxicity in all cases. In addition, most patients had negative findings on illicit drug screens.

Loperamide-related toxicities

Table 3 illustrates the different initial presenting toxicities associated with loperamide, as discussed in the published case reports. Death was the leading toxicity in both periods, but more gastrointestinal toxicities were reported during 1985-2013. More cardiovascular toxicities were reported between 2014 and 2016. Increasing recognition of loperamide misuse associated with cardiovascular effects may contribute to the increase in reporting of cardiotoxicity.

Most patients seen at a hospital survived upon discontinuation of loperamide. Seven patients died during their initial hospital admission: 4 during 1985-2013 and 3 during 2014-2016. This does not include the 19 cases of loperamide-related deaths reported by the NC OCME, as the patients in that report were all found dead before they could be transported to a hospital.

The majority of the patients that died during 1985-2013 reported that their rationale for loperamide use was gastrointestinal symptom relief. During 2014-2016, the patients who died at initial hospital presentation were taking prescription narcotic pain medications, with 2 of those 3 patients taking buprenorphine concomitantly with loperamide. In addition to the 3 deaths that occurred at the initial hospital admission during 2014-2016, 2 more patients died at a subsequent hospital admission after the initial hospital discharge. The main reason given for loperamide use by the patients that died during 2014-2016 was use of loperamide as an opioid alternative, and most had a significant history of substance use disorder.

Of the 7 patients who died in the case reports between 1985 to 2016, 4 of them were on at least 1 medication that posed an increased risk of causing QT prolongation. Loperamide itself at high doses can cause QT prolongation; therefore, it should be used with caution with other medications that can also prolong the QT interval. It is also important to note that of the 7 patients who died in the case reports during 1985-2016, 5 of the patients had cardiotoxicity at hospital admission.

Loperamide overdose and drug concentrations

The dose and scheduling frequency of loperamide taken by the patients were not documented in detail in the case reports leading to death. However, 3 of the patients who died had loperamide drug blood levels drawn post mortem and had loperamide drug concentrations ranging 63-140 ng/mL (therapeutic loperamide normal range <2 ng/mL).[49] In the 19 loperamide-related deaths reported by the NC OCME, the average blood concentration of loperamide was 270 ng/mL. These supratherapeutic levels suggest that massive quantities of loperamide were ingested. Some case reports have suggested the patients were using up to 400 mg (200 capsules) of loperamide per day.[19]

Management of overdose

Standard principles of overdose management should be performed. If loperamide is suggested or confirmed as an offending agent, management of respiratory depression or ventricular dysrhythmias must be considered.

Naloxone was used for reversal in 3 case reports. Of the patients who died, naloxone was given to 2 patients without success. One patient exhibited a cardiac arrhythmia while the other exhibited hypotension and respiratory depression. The patient with hypotension was also given sodium bicarbonate in addition to naloxone. A 4-month-old girl was inadvertently given approximately 2 mg/kg loperamide liquid; she subsequently became comatose with respiratory depression.[50] She recovered after repeated injections of naloxone for 24 hours.

While naloxone might reverse respiratory depression induced by opioids, it would not be expected to affect cardiotoxicity associated with loperamide as cardiotoxicity appears to be independent of its opioid properties. In addition, there have been occurrences of arrhythmias and cardiac arrest reported after administering naloxone; these occurred predominantly in patients who had pre-existing cardiovascular disorders or received drugs which may have had similar cardiovascular toxicities.[51]

Cardiopulmonary resuscitation and advanced cardiac life support measures should be used for patients in cardiopulmonary arrest after a loperamide overdose.[13] Naloxone would be a reasonable choice for respiratory depression, while intravenous sodium bicarbonate and magnesium sulfate can be used to manage ventricular dysrhythmias, including polymorphic ventricular tachycardia.[7,28] For QTc prolongation, intravenous isoproterenol, transcutaneous electrical pacing, and transvenous pacing have been used.[19,36,38]

Discussion

Loperamide may be appealing to opioid users seeking either opioid replacement or euphoria for several reasons. Large quantities are readily available through retail and Internet outlets. Anecdotal user experiences and suggestions for dosing regimens and synergistic adjuncts are readily found on various websites. A 2013 study of a single website that hosted illicit drug discussions found almost 1300 postings from 2005 to 2011.[8] Loperamide is not detected in routine urine drug screening for opioids but requires a blood sample and special request for testing.[52]

Following a single oral dose of 2 mg, serum levels remain <2 ng/mL.[49] In drug overdose deaths, the mean serum level was 270 ng/mL, indicating intake of 100 or more 2-mg capsules.[26] Because reports of loperamide misuse and deaths are increasing, the fact that large quantities seem to be readily available should sound an alarm for pharmacists.

One potential way to reduce loperamide misuse is to limit its availability to users, much like the way the federal government limited pseudoephedrine availability with the Combat Methamphetamine Epidemic Act of 2005.[53] This act limited package sizes and the maximum quantity that could be sold, placed them behind the counter, and required records of pseudoephedrine purchases by customers. Unfortunately, after initial success was achieved in limiting availability for methamphetamine production, criminals resorted to paying networks of individuals to purchase products from multiple outlets.[53] As a result, some states have increased restrictions on pseudoephedrine sales, including scheduling them as Schedule III controlled substances requiring a prescription.

Limitations

This review is based on reported cases of loperamide misuse, and aggregate results reflect the limited case information available. No epidemiologic studies are available to characterize the extent of misuse, and no data was found describing the extent of loperamide sales.

Conclusion

The use of loperamide as an opioid alternative is increasing. Although loperamide toxicity can lead to gastrointestinal, respiratory, and neurologic consequences, cardiac arrhythmias including QTc prolongation are potentially fatal. Adverse events have been described with loperamide alone or in combination with other medications. Although loperamide toxicity has been reported in multiple demographics, young adult men with a history of substance use disorder appear to be at highest risk. The Internet hosts several forums in which users report how to use loperamide to ameliorate opioid withdrawal symptoms and to achieve euphoric states. Health care professionals, including pharmacists, need to be aware of the potential for loperamide misuse, and they should consider loperamide toxicity in patients with the signs and symptoms described herein. We suggest that loperamide products be available "behind the counter" on request to the pharmacist to monitor sales. Increased government restrictions on nonprescription loperamide may be considered.

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