U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

FDA warns about serious heart problems with high doses of the antidiarrheal medicine loperamide (Imodium), including from abuse and misuse

Safety Announcement

[6-7-2016] The U.S. Food and Drug Administration (FDA) is warning that taking higher than recommended doses of the common over-the-counter (OTC) and prescription diarrhea medicine loperamide (Imodium), including through abuse or misuse of the product, can cause serious heart problems that can lead to death. The risk of these serious heart problems, including abnormal heart rhythms, may also be increased when high doses of loperamide are taken with several kinds of medicines that interact with loperamide (see Examples of Drugs that Can Potentially Interact with Loperamide).

The majority of reported serious heart problems occurred in individuals who were intentionally misusing and abusing high doses of loperamide in attempts to self-treat opioid withdrawal symptoms or to achieve a feeling of euphoria. We continue to evaluate this safety issue and will determine if additional FDA actions are needed.

Health care professionals should be aware that use of higher than recommended doses of loperamide can result in serious cardiac adverse events. Consider loperamide as a possible cause of unexplained cardiac events including QT interval prolongation, Torsades de Pointes or other ventricular arrhythmias, syncope, and cardiac arrest. In cases of abuse, individuals often use other drugs together with loperamide in attempts to increase its absorption and penetration across the blood-brain barrier, inhibit loperamide metabolism, and enhance its euphoric effects. If loperamide toxicity is suspected, promptly discontinue the drug and start necessary therapy. If loperamide ingestion is suspected, measure blood levels, which may require specific testing. For some cases of Torsades de Pointes in which drug treatment is ineffective, electrical pacing or cardioversion may be required.

Advise patients taking loperamide to follow the dosing recommendations on the label because taking higher than recommended doses, either intentionally or unintentionally, may lead to abnormal heart rhythms and serious cardiac events leading to death. Also advise patients that drug interactions with commonly used medicines also increase the risk of serious cardiac adverse events. Refer patients with opioid use disorders for treatment (see Additional Information for Health Care Professionals).

Patients and consumers should only take loperamide in the dose directed by their health care professionals or according to the OTC Drug Facts label. Do not use more than the dose prescribed or listed on the label, as doing so can cause severe heart rhythm problems or death. If your diarrhea lasts more than 2 days, stop taking loperamide and contact your health care professional. Seek medical attention immediately by calling 911 if you or someone taking loperamide experiences any of the following:

- Fainting
- Rapid heartbeat or irregular heart rhythm
- Unresponsiveness, meaning that you can't wake the person up or the person doesn't answer or react normally

Ask a pharmacist or your health care professional if you are not sure how much loperamide to take, how often to take it, or whether a medicine you are taking may interact with loperamide. Always tell your health care professionals about all the medicines you are taking, including OTC medicines (see Examples of Drugs that Can Potentially Interact with Loperamide).

Loperamide is approved to help control symptoms of diarrhea, including Travelers' Diarrhea. The maximum approved daily dose for adults is 8 mg per day for OTC use and 16 mg per day for prescription use. It is sold under the OTC brand name Imodium A-D, as store brands, and as generics.

In the 39 years from when loperamide was first approved in 1976 through 2015, FDA received reports* of 48 cases of serious heart problems associated with use of loperamide. This number includes only reports submitted to FDA, so there are likely additional cases about which we are unaware. Thirty-one of these cases resulted in hospitalizations, and 10 patients died. More than half of the 48 cases were reported after 2010. The serious heart problems occurred mostly in patients who were taking doses that were much higher than recommended. In other cases, patients were taking the recommended dose of loperamide, but they were also taking interacting medicines, causing an increase in loperamide levels. Additional cases of serious heart problems associated with the use of loperamide were reported in the medical literature.[1-9] Cases reported to FDA and in the medical literature indicate that individuals are taking significantly high doses of loperamide in situations of both misuse and abuse, often attempting to achieve euphoria or self-treat opioid withdrawal. They are also combining loperamide with interacting drugs in attempts to increase these effects.

We urge patients, consumers, and health care professionals to report side effects involving loperamide or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

*The cases were reported to the FDA Adverse Event Reporting System (FAERS).

Examples of Drugs that Can Potentially Interact with Loperamide*

**This is not a complete list, and the extent of the effects of each drug are unknown. If you are not sure if a medicine you are taking interacts with loperamide, ask a pharmacist or your health care professional.*

Generic Name	Examples of Brand Name(s)
cimetidine	Tagamet HB
clarithromycin	Biaxin, Prevpac
erythromycin	E.E.S., Ery-Tab, Eryc, Eryped, PCE
gemfibrozil	Lopid
itraconazole	Onmel, Sporanox
ketoconazole	Available by generic only
quinidine†	Nuedexta
quinine†	Qualaquin
ranitidine	Zantac
ritonavir	Kaletra, Norvir, Technivie, Viekira Pak

†Quinine and its isomer quinidine are also present in Tonic Water.

Facts about loperamide

- Loperamide is approved to help control symptoms of diarrhea, including Travelers' Diarrhea. It is sold over-the-counter (OTC) under the brand name Imodium A-D, as store brands, and as generics. The majority of single-ingredient loperamide sold in the U.S. is OTC. It is also available by prescription.
- Loperamide acts on opioid receptors in the gut to slow down the movement of the intestines. This decreases the number of bowel movements and makes stools less watery.
- Loperamide is approved for use in single doses of 4 mg for the first dose followed by 2 mg after each loose stool for adults. The maximum approved total daily dose is 8 mg per day for OTC use and 16 mg per day for prescription use.
- Dosing for children depends on the age of the child. Loperamide is not recommended for use in children younger than 2 years.
- Loperamide is available as a tablet, capsule, or liquid to take by mouth. Although it is usually taken after each loose stool, it is important not to exceed the total daily dose that is recommended on the drug label or prescribed by your health care professional.
- Common side effects include dry mouth, dizziness, drowsiness, stomach discomfort, nausea or vomiting, and constipation.
- Loperamide can interact with antifungal drugs such as itraconazole and ketoconazole; the cholesterol drug gemfibrozil; the heart drug quinidine; the antimalarial drug quinine; the HIV drug ritonavir; drugs to treat acid reflux including histamine type 2 receptor antagonists (H2RAs); and the antibiotics erythromycin and clarithromycin (see Examples of Drugs that Can Potentially Interact with Loperamide). Any of these drugs when taken with loperamide can increase loperamide blood levels.

Additional Information for Patients and Consumers

- Taking higher than the recommended dose of the antidiarrheal medicine loperamide can lead to serious heart problems, including abnormal heart rhythms and death. Use no more than the dose of loperamide listed on the label or prescribed by your health care professional.
- Taking loperamide with several kinds of commonly used medicines can increase the level of loperamide in the body and can raise the risk of these serious heart problems and death, especially if you take more than the recommended dose of loperamide. See Examples of Drugs that Can Potentially Interact with Loperamide.
- Always tell your health care professionals about all the medicines you are taking, including over-the-counter (OTC) medicines, vitamins, and other supplements.
- Seek medical attention immediately if you or someone taking loperamide experiences any of the following: fainting; rapid heartbeat or irregular heart rhythm; or unresponsiveness, meaning that you can't wake the person up or the person doesn't answer or react normally.
- Always read the Drug Facts labels included on all OTC medicines to find out how much and how often you should take them and if the medicines contain loperamide.
- If you are not sure how much loperamide to take, how often to take it, or whether a medicine you are taking interacts with loperamide, ask a pharmacist or your health care professional.
- Stop taking loperamide and contact your health care professional if your diarrhea lasts more than 2 days, your symptoms get worse, or you get abdominal swelling or bulging.
- Do not give loperamide to a child younger than 2 years unless directed by a health care professional.
- Report side effects from loperamide or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Additional Information for Health Care Professionals

- Higher than recommended doses of loperamide can cause serious cardiac events, including QT interval prolongation, Torsades de Pointes, other ventricular arrhythmias, cardiac arrest, syncope, and death.
- Consider loperamide as a possible cause of these unexplained cardiac events. In some reported cases, these events were not attributed to loperamide, resulting in ineffective and/or delayed treatment.
- If loperamide-induced cardiotoxicity is suspected, promptly discontinue loperamide and start therapy to manage and prevent cardiac arrhythmias and severe outcomes.
- Measure blood levels of loperamide. Standard drug screens for opioids do not include an assay for loperamide; such testing for opioids will yield negative

results even in the presence of loperamide. If you need to measure blood levels of loperamide, specifically request the test.

- Consider electrical pacing or cardioversion for loperamide-associated Torsades de Pointes that persists despite pharmacotherapy. In many reported cases, antiarrhythmic medications were ineffective, and electrical pacing or cardioversion were required to control the arrhythmias.
- In the majority of severe cases, individuals intentionally abused loperamide by taking massive doses to achieve a feeling of euphoria or prevent opioid withdrawal. Some patients also misused loperamide by taking higher than recommended doses to treat diarrhea. In the most severe cases, individuals self-treated with doses ranging from 70 mg to 1600 mg daily, which is 4 to 100 times the recommended dose.
- In several cases, individuals used concomitant drugs to increase gastrointestinal absorption, decrease loperamide metabolism, and increase blood brain barrier penetration. These drugs included CYP3A4 inhibitors (e.g., intraconazole, clarithromycin), CYP2C8 inhibitors (e.g., gemfibrozil), and P-glycoprotein inhibitors (e.g., quinidine).
- With loperamide abuse, concomitant use of drugs that inhibit CYP3A4, CYP2C8, and/or P-glycoprotein may increase the risk of serious cardiac events. Multiple drugs that act on different metabolic or transporter pathways may act synergistically to increase loperamide concentrations. See Examples of Drugs that Can Potentially Interact with Loperamide.
- Loperamide is an opioid that has relatively low gastrointestinal absorption and poor blood-brain barrier penetration. At approved doses, loperamide has a relatively long half-life of 9 to 13 hours. At doses of 16 mg and higher, the half-life has been found to be as high as 41 hours.
- Prescribe loperamide with caution in patients who are predisposed to QT interval prolongation, Torsades de Pointes, and other serious arrhythmias or who are on drugs that inhibit loperamide metabolism or transport (i.e., CYP3A4, CYP2C8, or P-glycoprotein inhibitors). Concomitant drugs may act synergistically to increase loperamide concentrations by blocking more than one pathway of loperamide elimination.
- Counsel patients about the cardiac risks of loperamide and tell them not to use more than the recommended dose.
- Refer patients with opioid use disorders for treatment. There are FDA-approved drugs to reduce opioid withdrawal symptoms.
- Loperamide is not recommended for use in children under 2 years.
- Report adverse events involving loperamide or other drugs to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.

Data Summary

A search of the FDA Adverse Event Reporting System (FAERS) database from December 28, 1976 (initial FDA approval), through December 14, 2015, identified 48 cases of serious cardiac events with loperamide use. The most frequently reported

cardiac events were syncope (n=24), cardiac arrest (n=13), QT interval prolongation (n=13), ventricular tachycardia (n=10), and Torsades de Pointes (n=7). Some cases reported more than one cardiac event. Ten cases resulted in death. Nine of the deaths were due to ingestion of large amounts of loperamide, and there was one sudden cardiac death after the patient ingested an unknown amount of loperamide. In many cases, standard antiarrhythmic medications were ineffective and only electrical pacing resulted in control of the arrhythmias.

Twenty-two of the 48 cases reported that the patients were abusing high doses of loperamide, and 17 cases reported that the patients were taking loperamide to treat diarrhea. Among the 17 patients who used loperamide for diarrhea, 11 reported taking therapeutic doses of loperamide, 5 reported using higher than recommended doses, and 1 did not report a loperamide dose. Of the cases that reported a loperamide dose, the mean dose was 195 mg per day (range 1 to 1600 mg per day). Of the cases that reported the duration of loperamide use, the duration ranged from less than 1 day to 18 months. Among the 11 cases that reported therapeutic doses, 2 were in children younger than 2 years, in whom loperamide use is not recommended. One child experienced syncope and hypoventilation, and the other experienced ventricular tachycardia.

Several of the 48 cases indicated the patients were intentionally misusing concomitant drugs that are cytochrome P450 (CYP3A4 or CYP2C8) or P-glycoprotein inhibitors, such as quinidine, which have the potential for drug-drug interactions with loperamide that can increase the blood levels and the effects of loperamide. Four of these cases included patients taking recommended doses of loperamide. Seventeen of the 48 cases had a positive dechallenge following the discontinuation of loperamide, and 5 cases had a positive rechallenge with the reintroduction of loperamide. Of the five rechallenge cases, four were Torsades de Pointes and one was ventricular arrhythmia.

Twelve cases of Torsades de Pointes (seven were reported as Torsades de Pointes and five were clinically consistent with it) and 11 of the 13 cardiac arrest events (including 8 cases resulting in deaths) occurred with loperamide abuse or misuse. In contrast, syncope and ventricular tachycardia events occurred when patients took therapeutic doses of loperamide.

We also searched the medical literature and identified additional cases of serious cardiac events with loperamide.[1-5] One case resulted in death, one was loperamide-induced Brugada syndrome, and three were Torsades de Pointes after ingesting large doses of loperamide. In all three Torsades de Pointes cases, the patients self-treated their chronic diarrhea with massive doses of loperamide (range 144-192 mg per day). Multiple advanced measures such as defibrillation and pacemaker insertion were needed. Since our review, four additional articles describing serious cardiac events with loperamide have been published, including two that resulted in death.[6-9]

Data from U.S. poison control call centers indicate that since 2006, and particularly since 2010, calls have increased for intentional loperamide exposures, which include cases of intentional abuse, intentional misuse, suspected suicide attempt, and unknown intentional

exposures. Similar increases were not seen for the prescription-only antidiarrheal product diphenoxylate/atropine.[10] The total number of fatal poisonings nationally that document antidiarrheal drugs as a cause of death has increased since 2012 but remains low.[11] However, because loperamide testing is not included in routine toxicology testing and may not be recognized as the drug causing or contributing to a death, these numbers may be an underestimate of actual deaths due to loperamide poisoning.

References

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Related Information

- The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective
- Think It Through: Managing the Benefits and Risks of Medicines