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Toxicology Rounds

Toxicology Rounds: Opioid Abusers Using Loperamide to Get High or Alleviate Withdrawal, with Fatal Consequences

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Loperamide, an opioid antidiarrheal medication, is, surprisingly, the latest drug of abuse, and was recently held accountable for two deaths in New York.

Figure. Some Drugs t...

Loperamide (Imodium) acts on mu-opioid receptors in the intestinal wall to inhibit gastrointestinal motility and decrease frequency of loose stools. The medication was approved by the Food and Drug Administration in 1976, and quickly became a best-selling prescription drug.

Many patients (and clinicians) still feel that loperamide is safe and, at best, a weak opioid. An important recently published paper demonstrates that neither of those beliefs is actually true.

Loperamide Abuse Associated with Cardiac Dysrhythmia and Death

Eggleston W, Clark KH, Marraffa JM

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The authors report two fatal cases associated with loperamide abuse. The first involved a 24-year-old man who was found pulseless and apneic at home. Paramedics reported seeing six empty boxes of loperamide at the scene. Resuscitative efforts in the field and in the hospital failed. An autopsy revealed a central blood loperamide level of 77 ng/mL (therapeutic, 0.24-1.37 ng/mL). It was later discovered that the young man had been taking loperamide to treat opioid-withdrawal symptoms.

The second case described a 39-year-old man who collapsed at home and could not be resuscitated. His family reported a history of opioid dependence that he was self-treating with loperamide. The post-mortem peripheral blood loperamide level was 140 ng/mL.

Poison center data and discussions in online drug forums over the past several years have indicated that some opioid abusers have been taking massive — and I mean massive — amounts of loperamide, sometimes to get high but most frequently to alleviate withdrawal symptoms. The recommended dose of loperamide is one to sixteen 2 mg pills a day, but some reports have described patients ingesting up to 300 pills each day for weeks or months on end.

P-gp can be thought of as a chemical bouncer tasked with keeping troublemaking drugs and substances out of important areas of the body. This biological Mr. T is found in the intestinal wall where it uses power from ATP to pump loperamide back into the gut, preventing it from being absorbed systemically. That is why a typical dose of loperamide has a bioavailability of only about 0.3%.

Loperamide overdose can present with CNS and cardiac toxicity. CNS manifestations include typical signs of the opioid toxidrome such as impaired cognition, respiratory depression and miosis. Numerous case reports of loperamide toxicity also describe QRS and QTC prolongation and ventricular dysrhythmias. Several patients have recently been worked up for unexplained syncope that in retrospect was attributed to loperamide-induced cardiotoxicity.

The drug seemed to be safe, at least in adults, at therapeutic doses (2-16 mg per day), with only minor adverse effects such as nausea. No major toxicity or central opioid manifestations were reported. Patients taking recommended doses did not experience euphoria, respiratory depression, lethargy, or mental status impairment. In fact, loperamide was deemed so safe by 1988 that it got the green light to be sold over-the-counter.

How can we explain these fatalities from abuse of a supposedly safe over-the-counter antidiarrheal preparation? Why are we just seeing these cases now, when loperamide itself has been available for four decades? Are we likely to see more patients presenting with serious toxicity from loperamide?

It is easy — and not very expensive — to acquire that much loperamide. Costco sells a box of 400 2 mg loperamide caplets for $7.59. No wonder the drug is sometimes called the "poor man's methadone."

Loperamide as an opioid agonist is not really weak at all; that's why it is an effective agonist at the mu-opioid receptors in the gut wall. But the drug doesn't cause typical opioid toxicity, at least when taken in therapeutic doses, because it has a difficult time getting into the brain. To understand why, you have to appreciate the function of the P-glycoprotein (P-gp) in the cell membrane.

P-gp is also part of the blood-brain barrier, protecting the central nervous system (CNS) by ejecting back into the circulation any small amount of loperamide that manages to make it that far. Massive doses of the drug, however, can overwhelm these protective mechanisms.

Ingeniously, street pharmacologists have figured out that a number of medications inhibit the action of P-gp, and some patients will ingest large amounts of loperamide along with one of these inhibitors to enhance the opioid effect. (Table.)

The mainstay in treating massive loperamide overdose is good supportive care. Early reports of pediatric toxicity suggest naloxone is effective in reversing respiratory depression, but it can precipitate acute withdrawal in an opioid-dependent patient, so intubation and mechanical ventilation might be preferable. Loperamide is fat soluble, and lipid rescue therapy should provide a theoretic benefit, although I could not find a convincing case report that demonstrated this. It is important to consider loperamide abuse when a patient presents with

unexplained syncope, ventricular dysrhythmias, or prolongation of the QRS and QT intervals.

Our group consulted on an interesting case many years ago. A 27-year-old man was found apneic and without a pulse in his hotel room near the airport. A number of empty packages of loperamide were found at the scene, and it was assumed the cause of death was loperamide overdose. Autopsy revealed, however, that his gut contained dozens of condoms full of heroin, one of which had broken and killed him The patient, a drug mule, had recently flown in from South America, and was taking loperamide so he wouldn't pass the packets before going through customs.

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