



## H140 Loperamide Intoxication: Case Reports and a Review of the Literature

Paul Uribe, MD\*, Martin Army Community Hospital, Fort Benning, GA 31905

**Learning Overview:** After attending this presentation, attendees will (1) better understand the pharmacology and physiology of loperamide toxicity, (2) know the incidence of use and misuse of this drug for managing opiate withdrawal symptoms, and (3) be aware of the implications of the 2016 adverse side effect ruling on loperamide by the Food and Drug Administration (FDA).

**Impact on the Forensic Science Community:** This presentation will impact the forensic science community by increasing awareness of the growing problem of toxicity and lethality of this readily available over-the-counter medication.

Loperamide is a readily available and increasingly abused over-the-counter anti-diarrheal medication that is a growing cause of medication-related fatalities in the United States. In higher doses, loperamide can produce side effects of cardiotoxicity, cardiac arrhythmias, euphoria, and central nervous system depression. Loperamide is a  $\mu$ -opioid receptor agonist that is metabolized by the cytochrome P450 system.<sup>1</sup> Loperamide has low bioavailability in appropriate doses, and therefore has limited central nervous system activity due to the limited ability to cross the blood-brain barrier. In higher doses, the drug can penetrate the central nervous system and lead to tolerance and, upon cessation of use, withdrawal symptoms. The arrhythmogenic side effects include syncope, QT-interval prolongation, QRS-interval widening, torsade de pointes, ventricular dysrhythmias, and cardiac arrest.<sup>2</sup> Loperamide is increasingly used, and misused, as an inexpensive, readily available, over-the-counter alternative for self-managing the symptoms of opiate withdrawal, including withdrawal from methadone.<sup>2-4</sup>

From 2010 to 2015, there was a 91% increase in reported loperamide abuse.<sup>5</sup> Between 2002 and 2015, 224 adults were referred to a health care facility for intentional ingestions of loperamide as reported to the poison control system.<sup>6</sup> During this period, there were 15 reported deaths involving loperamide, with over half involving single-agent loperamide abuse. There was a spike in the number of cases between 2014 and 2015, which coincided with plentiful online instructions on how to abuse this drug. The availability and misuse of loperamide has resulted in the FDA issuing a warning about the adverse side effects in June 2016.<sup>7</sup> This warning was based on 48 cases of severe cardiac side-effects associated from loperamide misuse from the approval date of loperamide of December 1976 through December 2015, with more than half of the cases reported after 2010.

Depending on what toxicology screens are available, loperamide may be overlooked as routine drug screen panels may not detect this drug. It may also be clinically overlooked in routine drug testing for drug-treatment program compliance. Thorough scene investigation may overlook this relatively innocuous medication. Clinical awareness of this entity is critical to early recognition and treatment. Two unexpected deaths from acute loperamide intoxication are discussed and followed by a discussion of the pharmacology, side-effects, and abuse trends involving this readily available over-the-counter medication.

### Reference(s):

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### Loperamide, Toxicology, Cardiotoxicity