CASE REPORT

Loperamide dependence and abuse

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SUMMARY

Loperamide is a common over-the-counter antidiarrheal considered safe in a broad range of dosages and thought devoid of abuse potential. We describe the first case of a patient with loperamide dependence due to misuse of its opiate-like effects achieved by chronic massive oral ingestions. A 26-year-old man who was taking 800 mg of loperamide per day presented requesting detoxification referral. Loperamide has potential for euphoric effects and information on how to facilitate such effects is easily available. It is important for physicians to be aware of the potential for misuse of and dependence on loperamide, with symptoms mimicking opiate use.

BACKGROUND

Loperamide is a commonly used antidiarrhoeal considered safe over a range of dosages.[1 2] Available over-the-counter in the US since 1988, loperamide is considered devoid of abuse potential because of rapid metabolism and poor blood–brain barrier penetration.[2] Rare reports of opiate-like adverse effects responding to naloxone have been reported, primarily after large oral overdoses in young children.[1] To date, there are no reports of abuse for its opiate-like abuse but there is evidence from internet searches that such use is increasing. It is important for physicians to be aware of the potential for misuse of and dependence on loperamide, with symptoms mimicking opiate use.

CASE PRESENTATION

A 26-year-old man presented to our emergency department requesting detoxification referral for loperamide dependence. He reported development of prescription opiate abuse beginning at age 17, later using alternative sources of opiates for both euphoria and to avoid withdrawal symptoms, including extraction from supermarket poppy seeds with citric acid. From internet recommendations, he also began experimenting with loperamide, ultimately leading to ingestion of 800 mg daily to achieve an opiate-like effect. For more than 18 months, he had been taking 100 2 mg capsules two times per day, increasing slowly to his current dose of 200 2 mg capsules two times per day. Failed attempts to discontinue loperamide produced severe withdrawal symptoms including diaphoresis, anxiety, tremor, yawning, vomiting, watery eyes and diarrhoea. He denied other current drug use but noted that he had recently been denied detoxification services for loperamide dependence; he therefore took prescription narcotics to create a positive toxicology result and gain admission for narcotic addiction. He had failed that detoxification and abstinence attempt. His medical history was significant for Brugada Syndrome with automatic implantable cardioverter defibrillator placement; he took no medications. He was married and denied illicit substance use, alcohol or tobacco. His vital signs were normal and his physical examination was unremarkable without evidence of toxidrome or withdrawal.

OUTCOME AND FOLLOW-UP

The patient was admitted to an inpatient opiate detoxification programme. He left voluntarily the next day. Four days later the patient was brought back to the emergency department after being found in cardiac arrest with a rhythm of pulseless electrical activity. He was resuscitated and admitted to the intensive care unit where he gained consciousness long enough to admit to a suicide attempt via loperamide overdose. He ultimately died during this admission. Initial urine screen for drugs of abuse was negative; on autopsy, only loperamide at the upper therapeutic levels (2 days after presentation) was found. A specific cause of death was never determined.

DISCUSSION

Loperamide is a potent μ-opioid receptor agonist with predominantly peripheral activity, low bioavailability and poor blood–brain barrier penetration. Loperamide exhibits opiate agonist effects on the myenteric plexus, primarily increasing intestinal transit time by decreasing propulsive activity. Secondary peripheral effects are seen at κ-opioid and δ-opioid receptors.[3] This receptor activity prompted the US Food and Drug Administration to place loperamide in Schedule V of the Controlled Substance Act in 1977. Subsequent studies, including administration of up to 60 mg, supported its safety and low physical dependence risk.[4 5] By 1988, loperamide was no longer scheduled and had been made available for over-the-counter use in the USA.

Despite loperamide's low side effect profile, a 26-year-old patient with anxiety about diarrhoea was reported to use 320 mg daily for several months without euphoric effects but with symptoms of narcotic withdrawal on discontinuation; he required methadone treatment to facilitate cessation.[6] The case reported here is the first of a patient with significant loperamide dependence on its euphoric effects.

Loperamide's effect on the central nervous system (CNS) has most notably been described in children, including a 4-month-old with 'severe depression of consciousness, bradypnoea and miosis' and symptom resolution after naloxone

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treatment. This prompted US market withdrawal of concentrated loperamide solution and warnings against its use in children under the age of 3 years.[7 8] Loperamide may reach the CNS in cases where the 'blood–brain barrier is defective or immature',[9] a concept supported by studies demonstrating increased CNS activity after permeability alteration of the blood–brain barrier. Intravenous loperamide given to adult rats had no analgaesic effect when given alone; but when administered in conjunction with a bradykinin analogue to increase blood–brain barrier permeability, loperamide produced significant naloxone-reversible analgaesia.[10]

Adjuncts to facilitate increased loperamide CNS concentrations are easily achieved. Nasal inhalation of the drug or use with readily available ingestants such as grapefruit juice and cimetidine effectively bypass or inhibit first-pass metabolism by CYP3A4, increasing plasma levels.[11] Easily available P-glycoprotein (P-gp) inhibitors such as pepper and quinine facilitate blood–brain barrier permeability.[3 12]

Resources for recreational drug use and suggestions for substance combinations to increase the euphoric effect of loperamide can easily be found online (eg, http://www.bluelight.ru; http://www.drugs-forum.com). Discussion threads regarding loperamide use for euphoria or relief of opiate withdrawal symptoms are common as are sophisticated protocols to facilitate high CNS concentrations. One user reported that she could remain 'high' for 12 h by ingesting 60 mg of loperamide along with cimetidine, grapefruit juice for P450 inhibition, and an energy drink containing quercetin and quinine for P-gp inhibition. Such online discussions are documented in the medical literature.[13 14]

Risks to organs other than the CNS from loperamide misuse, especially in combination with other drugs, is unknown. There is a clear theoretical risk of cardiac effects. As in other opioids, loperamide acts on vagal μ and δ receptors to decrease blood pressure and heart rate;[15] k-opioid receptor involvement may cause bradycardia with hypotension from a secondary decrease in cardiac output;[16] and loperamide directly blocks calcium channels in peripheral muscle.[17 18] Although the cause of death of our patient was complicated by his cardiac history and never definitively determined, there is, nevertheless, a case series of life-threatening ventricular arrhythmias temporally associated with loperamide misuse.[19]

While loperamide is not generally considered to be a drug of abuse, this report illustrates the potential for loperamide misuse and dependence. Existing lay strategies to increase the CNS effects of loperamide, and easy access to such strategies via the internet, may circumvent protection measures such as manufacturer drug concentrations. As such methods become more widely known, loperamide dependency, abuse and toxicity may become an increasing problem.

Physicians are likely to be a first point of contact between loperamide-abusing patients and the healthcare system, as they are for many drugs of abuse. In this case, the patient claimed that his requests for help had been rejected in the past due to the perceived safety profile of loperamide. Knowledge of its abuse potential may facilitate the ability to identify patients who could benefit from drug treatment referral or medications to alleviate symptoms of loperamide-associated opiate withdrawal.

Learning points

- Loperamide can be abused at high doses for its opiate-like effects.
- Various forums on the internet offer advice for drug combinations to increase the effects of loperamide use.
- Physicians should be aware of the risk of dependence and abuse of loperamide.

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