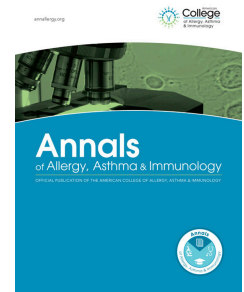


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An unusual case of loperamide anaphylaxis

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An unusual case of loperamide anaphylaxis

Letter – Revised

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A 75-year-old non-atopic male had been suffering from a gastroenteritis-like illness for the last 24 hours characterized by diarrhea and malaise. He decided to take, for the first time, 4 mg of loperamide hydrochloride to assist with symptom relief. Within 30 minutes, he developed severe anaphylaxis with widespread urticaria, presyncope and acute worsening of diarrhea and vomiting. He was transported by ambulance to the hospital, where his initial blood pressure was 82/50. He was successfully resuscitated with two doses of intramuscular epinephrine and intravenous saline.

The patient had not had any other oral intake apart from water and paracetamol several hours before the episode. His background history included hypercholesterolemia, type 2 diabetes mellitus, hypertension and gastro-esophageal reflux disease. His regular medications, which he did not take for more than 24 hours prior to the incident due to his anorexia, were irbesartan, empagliflozin/metformin, pantoprazole, cholecalciferol and magnesium. He had no recent changes in his medications. He had no prior opioid medication exposures; though admitted to trialing opium smoking as a once-off venture in his youth. He had no other known allergies to medications.

Excipients in loperamide had been tolerated in his other medications which he took for his metabolic syndrome.

Blood tests revealed an elevated tryptase of 15.3 µg/L (< 11.4) 5 hours post anaphylaxis onset with a subsequent baseline normal tryptase of 5.6 µg/L (ImmunoCAP, Phadia) more than 24 hours after the event. His specific IgE to morphine was undetectable (< 0.10 kU/L). Stool cultures did not reveal a causative microorganism. Despite hypotension and his comorbidities, he had essentially normal renal function.

Three months post discharge, *in vivo* skin testing was performed using published concentrations of maximum non-irritating concentrations.^{1,2} He had a positive intradermal test to both loperamide and its related opioid, fentanyl (Table 1). The maximum intradermal non-irritating concentration for loperamide (0.2 mg/mL) diluted in saline was confirmed on three healthy controls. The patient successfully underwent a subcutaneous challenge of a total dose of 20 µg alfentanil. He was subsequently advised to avoid loperamide, fentanyl and pethidine (not tested due to unavailability) indefinitely. An offer of basophil activation testing (BAT) has been declined by the patient.

Loperamide is an over-the-counter pethidine analogue that is commonly used as an anti-diarrheal agent. As an opioid agonist, it exerts its effects on μ opioid receptors primarily in the gut and decreases intestinal motility.³

The drug can be associated with a number of mild side-effects, such as abdominal bloating and constipation and is generally well tolerated. Loperamide hypersensitivity is rare and few case reports in the literature exist. One exists of a 34 year-old man who took a cumulative dose of 8 mg of loperamide in the setting of a 2-day history of gastroenteritis and developed severe anaphylactic shock with cardiac arrest before dying.⁴ At post mortem, he was found to have undiagnosed severe coronary artery disease, a likely significant contributor to his death.

Another case occurred in a 10 year-old boy who had previously tolerated loperamide.² Five minute post ingestion, he developed rash, eyelid angioedema, rhinorrhea and bronchospasm treated with glucocorticoids and antihistamines. Intradermal testing one year later was positive to loperamide at 0.02 mg/mL.²

A 48 year-old female developed delayed-onset anaphylaxis (angioedema, urticaria and respiratory distress) some 18 hours after loperamide ingestion which was confirmed on rechallenging. The authors wondered about possible altered bowel habits during gastroenteritis that affect systemic absorption or even a direct mast cell degranulation mechanism.⁵ Indeed, loperamide is directly absorbed through the gut and is rapidly metabolized via the cytochrome P450 family in the liver, meaning very little intact drug reaches the circulation.⁶ In instances of gastroenteritis, increased stomach emptying may enhance systemic absorption in the small intestine.⁷ For our patient, an empty stomach, relative dehydration and his age may have been factors to the initiation and severity of his allergic reaction.

Uniquely, our report is the first to show potential cross-sensitization with fentanyl through skin testing (Table 1), whilst others have found negative fentanyl skin tests.² Due to his age and comorbidities, we did not elect to confirm this potential cross-reaction through drug provocation testing (DPT), instead, using the alternative alfentanil. We also did not re-challenge with loperamide given the positive intradermal test and there was no pressing reason for the patient to take loperamide when clinically well.

Opioid hypersensitivity is thought to be due to a non-IgE-mediated mast cell degranulation via direct stimulation of mu opioid receptors.⁸ As a result, false positives are possible on intradermal testing, and concerns about the validity of performing *in vivo* skin testing has been raised.⁹ This has led some to argue about the greater adoption of DPT to avoid over-diagnosis and unnecessary avoidance of medications.¹⁰ Minimising the chances of false positives, we tested our loperamide concentrations on healthy volunteers and used authoritative published maximum non-irritating concentrations.¹

In summary, we report a unique case of loperamide anaphylaxis confirmed on intradermal testing with possible—but not confirmed— cross-sensitization to fentanyl. Loperamide anaphylaxis is a rare but potentially fatal complication of this relatively common over-the-counter drug and clinicians need to be aware of this complication. Although our patient had no pressing reasons to use opioid medications, we felt it important to establish opioid availability should he require this emergently in the future.

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96 **Table 1. Drugs and concentrations used for *in vivo* skin testing.**

	Skin prick testing		Intradermal testing 1		Intradermal testing 2	
	Concentration	Result	Concentration	Result	Concentration	Result
Loperamide	2 mg/mL	Negative	0.02 mg/mL	Negative	0.2 mg/mL	Positive
Oxycodone	0.1 mg/mL	Negative	0.01 mg/mL	Negative	0.1 mg/mL	Negative
Morphine	0.1 mg/mL	Negative	0.01 µg/mL	Negative	(Not tested)	
Alfentanil	50 µg/mL	Negative	0.005 mg/mL	Negative	0.05 mg/mL	Negative
Fentanyl	5 µg/mL	Negative	0.005 µg/mL	Positive	(Not tested)	
Saline 0.9%	Neat	Negative	Neat	Negative		
Histamine	10 mg/mL	Positive				

97

98