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Letter to the Editor

Delayed hypersensitivity reaction to loperamide: An intriguing case report with positive challenge test

Dear Editor,

Loperamide hydrochloride (Imodium®) is a symptomatic anti-diarrheal agent used for relieving acute and chronic diarrhea. It is an opiate derivative, which has no effects on central nervous system. Loperamide stops diarrhea via its negative effects on intestinal peristalsis and its mild antisecretory properties.¹ Loperamide is generally considered safe, but was in few cases the cause of anaphylaxis.

We report the case of a 48 year old female patient, with no relevant past medical or surgical history, who presented to allergy consultation in 2008 for a potential exploration of multiple drug allergy history. The patient described two possible immune-mediated allergic reactions that had occurred three years ago before, the first during an upper respiratory tract infection with a delayed generalized urticaria at day five of amoxicillin intake. The second episode was particularly severe and occurred during a gastroenteritis episode. In fact, eight to 10 h after taking diclofenac, paracetamol, pantoprazole and loperamide hydrochloride, she presented generalized urticaria, lips angioedema and dysphagia. Symptoms resolved within 2–3 h after parenteral administration of antihistamines and corticosteroids in the emergency department. Skin prick tests to diclofenac and amoxicillin were negative. Intradermal skin tests to amoxicillin and other penicillins were also negative. Then, oral challenge tests to diclofenac and amoxicillin were done and were both negative. The patient had re-taken paracetamol and pantoprazole without allergic symptoms after the episode. Because loperamide was considered an essential drug, it was not tested at the time and avoidance was recommended.²

The patient returned to the allergy consultation four years after the initial visit. Since her first reactions, she had presented four more episodes of generalized urticaria with lips angioedema occurring every time 8–12 h after taking loperamide and requiring visits to the emergency department. Her general practitioner prescribed loperamide without taking care of our first recommendation. Despite the fact that loperamide's responsibility in these different circumstances might have seemed obvious, we decided to perform an allergy work up for loperamide, especially due to the intriguing chronology; a non-immediate anaphylaxis. Skin prick tests (performed with 1 tablet of loperamide 2 mg/1 ml water) were negative, allowing us to proceed to the oral drug challenge test. Progressive incremental doses were administered till a total cumulative dose of 6 mg. Due to the severity and particular chronology of

the different episodes, we decided to keep the patient under hospital surveillance for 24 h. Eighteen hours after the beginning of oral challenge test to loperamide, the patient developed generalized urticaria, angioedema of the tongue and lips, dysphagia and respiratory distress. She was treated with adrenalin, corticosteroids and antihistamines. Respiratory symptoms resolved rapidly and cutaneous signs within three to 4 h.

In order to find an alternative to loperamide, we decided to test racecadotril, which is also an opiate derivative. Skin prick test to racecadotril was negative and it was followed by oral negative challenge test. Since the allergy work up, the patient has taken it twice without any allergic reaction.

Discussion

Rarely, specialized allergy explorations were done after an anaphylactic reaction due to loperamide. Only two cases of immediate IgE-mediated anaphylactic reaction to loperamide are published. Both cases consisted in a severe clinical presentation.^{3,4} In our patient, the duration before symptoms onset, eight to 10 h after taking loperamide was too long for considering an immune type 1 mediated hypersensitivity reaction. Surprisingly, the delay of 18 h before symptoms onset during the oral drug challenge, which is doubled in comparison to her “in real life episodes”, lead us to believe that other mechanisms could be involved. To the best of our knowledge, no other similar cases have been reported in the literature. After twenty years of experience in drug allergy work up and more than 3000 drug provocation tests performed, our experience is that about 95% of the reactions elicited during drug provocation tests are either of similar or sometimes of shorter chronology than that of the original case (data not published). Only rarely did the chronology during drug provocation test exceed the one of the initial reaction.

Hypotheses to explain the longer delay during the challenge test before symptoms begin are: (i) a decreased gastrointestinal permeability of normal mucosa and therefore delayed absorption of loperamide in comparison with infected mucosa during a gastroenteritis episode; no data are available to support this hypothesis, but it cannot be excluded; (ii) an intervention of others neurotransmitters and mediators than those released in immune IgE-mediated hypersensitivity; (iii) loperamide can induce hypersensitivity symptoms via opiates induced histamine release mechanism; in fact, this hypothesis is unlikely since the piperidine and phenylpiperidine group of opioid receptor agonists includes fentanyl, diphenoxylate, and loperamide that are structurally very different from

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morphine and studies suggest that this group does not cause direct histamine release.^{5,6}

We realized a review of the French Pharmacovigilance databases. We found 73 cases with a possible acute allergic reaction to loperamide. None of these reactions were explored by allergy skin tests, or by drug provocation tests. In the majority of these reports, loperamide was taken in the context of acute gastroenteritis. Then, it is reasonable to question, whether the viral infection and/or the damaged digestive mucosa would change the absorption and/or metabolism of loperamide; or if viral infection can promote faster digestive neurotransmitters release inducing hypersensitivity symptoms (acetylcholine, histamine...).

Conflict of interest

The authors have no conflict of interest to declare.

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