Omeprazole-induced urticaria: A selective hypersensitivity

Imen Bouaziz[1], Najah Ben Fadhel[1], Haifa Ben Romdhane[1], Nadia Ben fredj[1], Amel Chaabane[1], Zohra Chadli[1], and Karim Aouam[1]

[1]Fattouma Bourguiba University Hospital of Monastir

September 10, 2023

Abstract

Omeprazole is a proton pump inhibitor (PPI) that is indicated for gastroduodenal ulcer, gastroesophageal reflux and hypersecretory states. It has an excellent safety profile with a low incidence of adverse effects. We report an Omeprazole-induced urticaria in a patient and emphasize the role of allergological work-up to point out the culprit drug and in exploring cross-reactivity. A 56-year-old man with a history of Biermer anemia treated by vitamin B12. He has asthma and no other illnesses, allergic diseases or reactions, especially to drugs. He was treated with Omeprazole, for abdominal discomfort. Four hours after the first dose, the patient developed urticarial lesions with annular erythematous wheals localized on the trunk and upper limbs. There was neither angioedema nor respiratory and hemodynamic symptoms. An acute generalized urticaria to omeprazole was suspected. Four weeks later, Skin prick test than intradermal tests (IDT) to omeprazole were performed on the patient's forearm. They revealed respectively a negative and a positive result. To assess cross-reactivity to other PPIs in our patient, we subsequently performed prick test to lansoprazole and IDT to esomeprazole, and pantoprazole that were negative at 20-min reading. Moreover, graded oral provocation test with these drugs were carried out with negative result. In conclusion we add to the medical literature a case report of omeprazole-induced urticaria without a cross reactivity and point out the usefulness and safety of skin and provocation testing in diagnosing this drug reaction and in the assessment of cross-reactivity between PPIs. KEYWORDS: omeprazole, urticaria, cross-reactivity, selective hypersensitivity

Omeprazole-induced urticaria: A selective hypersensitivity

Imen Bouaziz (MD), Najah Ben Fadhel (MD), Haifa Ben Romdhane (MD), Nadia Ben Fredj (MD), Amel Chaabane (MD), Zohra Chadly (MD, PhD), Karim Aouam (MD, PhD)

Department of clinical pharmacology. University Hospital Fattouma Bourguiba of Monastir, Tunisia. University of Monastir, Tunisia.

Corresponding author

Imen Bouaziz

Tel: 0021620569425

Fax:

E-mail: imenbouaziz34@gmail.com

Financial relationship with a biotechnology and/or pharmaceutical manufacturer: NONE

Introduction

Omeprazole is a proton pump inhibitor (PPI) that is indicated for gastroduodenal ulcer, gastroesophageal reflux and hypersecretory states. It has an excellent safety profile with a low incidence of adverse effects.

Reported side effects of omeprazole are headache, constipation, diarrhea and, more rarely, elevated transaminases and hypersensitivity(1). Most of these latter reactions (86%) to PPIs seem to be IgE- mediated, and manifests clinically by urticaria, angioedema, hypotension, and dyspnea (2). Some sporadic cases of omeprazole-induced urticaria have been described in the medical literature and confirmed by skin tests considered as a reliable tool for establishing causality in the presence of concomitant drugs. Some case reports and studies have shown that cross-reactivity among PPIs does exist and is likely related to the similar organic structure of them(3). However, hypersensitivity could be selective to a single PPI. In this context, we report herein a clinical observation of omeprazole-induced urticaria without any cross-reactivity to other PPIs, confirmed by skin and provocation tests.

Case report

A 56-year-old man with a history of Biermer anemia treated by vitamin B12 since one year.

He has asthma and no other illnesses, allergic diseases or reactions, especially to drugs, consulted a private gastroenterologist because of abdominal discomfort. He had no fever, and the physical examination revealed no abnormality. The patient was prescribed 40 mg of omeprazole daily. Four hours after the first dose of omeprazole, the patient developed urticarial lesions with annular erythematous wheals localized on the trunk and upper limbs. There was neither angioedema nor respiratory and hemodynamic symptoms. The patient consulted urgently his gastroenterologist who considered the condition as acute generalized urticaria to omeprazole and prescribed cetirizine and dexamethasone, commenced immediately. The urticaria has disappeared entirely after an hour. Four weeks later the patient consulted in our department for investigating this episode of urticaria. Skin prick test (20mg/mL) than intradermal tests (IDT) (0.2 and 2 mg/mL) to omeprazole were performed on the patient's forearm according to the European Network of Drug Allergy recommendations. Histamine 10 mg/mL and 0.9% normal saline were used as positive and negative skin prick test controls, respectively. About ten minutes later, the patient had a strong reaction to omeprazole IDT 0.2 and 2 mg/mL. An IDT to omeprazole (0.2mg/ml) performed on two healthy controls according to the same procedure applied on the patient was negative. To assess cross-reactivity to other PPIs in our patient, we subsequently performed prick test to lansoprazole and IDT to esomeprazole (0.8mg/mL), and pantoprazole (0.4mg/mL) that were negative at 20-min reading. Moreover, graded oral provocation test with these drugs were carried out with negative result. OPTs with the alternative PPIs which had displayed negative results in the skin tests, were performed after his informed consent. During these tests, a lansoprazole capsule (15 mg), a pantoprazole tablet (20 mg), and an esomeprazole tablet (20 mg) were administered each on different days at 30-min intervals at increasing doses till reaching the full dose or the symptoms of a drug reaction occurred. These tests results were negative in all cases.

Discussion

We reported a clinical observation of a selective immediate hypersensitivity to omeprazole confirmed by skin and provocation tests. A clear temporal relationship was observed between omeprazole administration and the onset of symptoms; and the skin test to this drug was positive. Based on the Naranjo algorithm (4), it is probable that the urticaria was induced by omeprazole (Naranjo's score - 5). IgE-mediated reactions are the most frequently reported hypersensitivity reactions to PPIs (5). Urticaria was the most common clinical presentation in patients with immediate hypersensitivity reactions to PPIs after anaphylaxis (6). In our case, urticaria occurred four hours after omeprazole intake which is in line with literature. Indeed, immediate hypersensitivity reactions generally occur within a few hours after a dose, even though some case reports of delayed anaphylaxis to PPIs that occur between 2 and 24 hours after the intake of the latter drugs have been described (5,7). The incidence of hypersensitivity to omeprazole, the culprit PPI in our patient, is variable. For example, Kepil Özdemir et al. have reported a large series of 60 patients with PPIs-induced hypersensitivity reactions, and found that omeprazole was incriminated in only one patient (1.7%) after lansoprazole (68.3%), pantoprazole (20%), esomeprazole (10.%) and rabeprazole (6.7%) (7). In contrast, Tourillon et al. have found in 38 patients that omeprazole was the first culprit drug of immediate hypersensitivity reactions (33% vs. 23.8%, 23.8%, 11.9%, 7.2% for esomeprazole, pantoprazole, lansoprazole and rabeprazole, respectively) (8). Overall, 12 studies evaluating 395 patients with 416 immediate-type

hypersensitivity reactions to PPIs were identified. The main PPI elicitor of these reactions to PPIs was lansoprazole (40.6%) followed by omeprazole (26.2%), pantoprazole (15.6%), esomeprazole (14.4%), and rabeprazole (3.1%) (6).

The first case of hypersensitivity to omeprazole was described in 1994 by Bowlby and Dickens and the reaction was An anaphylactic shock (9). According to some studies, omeprazole was found to induce rarely anaphylaxis (10). in our patient, the diagnosis of omeprazole-induced urticaria was made possible by a positive skin test. This finding suggests that skin tests to this PPI are safe, as no systemic reaction was observed after the test. In case of PPI-induced IgE-mediated hypersensitivity reactions, many studies demonstrated that skin tests are a useful tool for the diagnosis (2). Kepil Özdemir et al. have analyzed the diagnostic value of skin tests in a group of 38 patients with PPI-induced immediate-type hypersensitivity reactions and in 30 healthy controls and found that specificity and positive predictive value of these tests were both 100%, and the sensitivity and negative predictive value were 58.8 and 70.8%, respectively (11,12) . Hence, we can confirm that the urticaria manifested by our patient was due to omeprazole as the concentration used in the test (0.2 and 2 mg/mL) was in accordance with the literature (13). Interestingly, in our case skin tests and oral provocation tests were all negative to esomepraole, lanzopraole and pantoprazole, suggesting a selective hypersensitivity to omeprazole. PPI have a common chemical structure composed by a benzimidazole and a pyridine ring but vary in the specific side-ring substitution (14). Accordingly, four general patterns of cross-reactivity have been identified: whole-group hypersensitivity, omeprazole -esomeprazole-pantoprazole hypersensitivity, lansoprazole-rabeprazole hypersensitivity, and selective sensitization to a single PPI (11). However, some studies have reported other patterns of cross-reactivity between PPIs such as lanzopraole-pantoprazole (7) and omeprazole-lanzoprazole(15–17). As the skin and provocation tests to lanzoprazole, pantoprazole and esomeprazole were negative in our patient, it could be argued that he has a selective hypersensitivity to omeprazole. Rabeprazole was not tested in our patient as not available in our country. To our knowledge we are the first describe a clinical observation of a type I hypersensitivity reaction to omeprazole without a cross reactivity to esomeprazole, pantoprazole and lansoprazole, confirmed by skin and drug provocation tests.

In conclusion we add to the medical literature a case report of omeprazole-induced urticaria and point out the usefulness and safety of skin and provocation testing in diagnosing this drug reaction and in the assessment of cross-reactivity between PPIs. Furthermore, we demonstrate the lack of cross-reactivity between omeprazole and esomeprazole, pantoprazole and lansoprazole. These PPIs could be safe alternatives in case of hypersensitivity to omeprazole.

References

1. Forgerini M, Mieli S, Mastroianni P de C. Safety assessment of omeprazole use: a review. São Paulo Med J. 13 déc 2018;136(6):557-70.

2. Lombardo C, Bonadonna P. Hypersensitivity Reactions to Proton Pump Inhibitors. Curr Treat Options Allergy. 1 juin 2015;2(2):110-23.

3. Lobera T, Navarro B, Del Pozo MD, Gonzalez I, Blasco A, Escudero R, et al. Nine cases of omeprazole allergy: cross-reactivity between proton pump inhibitors. J Investig Allergol Clin Immunol. 2009;19(1):57-60.

4. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. aout 1981;30(2):239-45.

5. Barakat L, Vasconcelos MJ, Bourrain JL, Demoly P, Chiriac AM. IgE-mediated allergy to proton pump inhibitors with both delayed and immediate onset. Asia Pac Allergy. 14 oct 2019;9(4):e30.

6. Kepil Ozdemir S, Bavbek S. Hypersensitivity reactions to proton-pump inhibitors: Clinical presentation, diagnosis, and management. Allergy Asthma Proc. 1 mars 2020;41(2):e37-44.

7. Kepil Ozdemir S, Oner Erkekol F, Unal D, Buyukozturk S, Gelincik A, Dursun AB, et al. Management

of Hypersensitivity Reactions to Proton Pump Inhibitors: A Retrospective Experience. Int Arch Allergy Immunol. 2016;171(1):54-60.

8. Tourillon C, Mahe J, Baron A, Lambert A, Yelehe-Okouma M, Veyrac G, et al. Immediate-Type Hypersensitivity Cross-Reactions to Proton Pump Inhibitors: A Descriptive Study of Data from the French National Pharmacovigilance Database. Int Arch Allergy Immunol. 2019;178(2):159-66.

9. Bowlby HA, Dickens GR. Angioedema and urticaria associated with omeprazole confirmed by drug rechallenge. Pharmacotherapy. 1994;14(1):119-22.

10. Ottervanger JP, Phaff RA, Vermeulen EG, Stricker BH. Anaphylaxis to omeprazole. J Allergy Clin Immunol. juin 1996;97(6):1413-4.

11. Otani IM, Banerji A. Immediate and Delayed Hypersensitivity Reactions to Proton Pump Inhibitors: Evaluation and Management. Curr Allergy Asthma Rep. mars 2016;16(3):17.

12. Kepil Ozdemir S, Yılmaz I, Aydin Ö, Büyüköztürk S, Gelincik A, Demirtürk M, et al. Immediate-type hypersensitivity reactions to proton pump inhibitors: usefulness of skin tests in the diagnosis and assessment of cross-reactivity. Allergy. août 2013;68(8):1008-14.

13. Pita JS, Azevedo J, Fernandes RA, Loureiro C, Bom AT. Immediate-hypersensitivity reactions to proton pump inhibitors. Ann Allergy Asthma Immunol. fevr 2019;122(2):204-5.

14. Confino-Cohen R, Goldberg A. Anaphylaxis to omeprazole: diagnosis and desensitization protocol. Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol. janv 2006;96(1):33-6.

15. Rojas Perez-Ezquerra P, Sanchez Morillas L, Laguna Martinez JJ, Davila Fernandez G, Prado Gomez-Tembleque M del, Santos Alvarez A, et al. Anaphylaxis to omeprazole. Cross-reactivity with the other proton pump inhibitors. Allergol Immunopathol (Madr). 1 janv 2011;39(1):54.

16. Galindo PA, Borja J, Feo F, Gomez E, Garcia R, Cabrera M, et al. Anaphylaxis to omeprazole. Ann Allergy Asthma Immunol. janv 1999;82(1):52-4.

17. Gonzalez P, Soriano V, Lopez P, Niveiro E. Anaphylaxis to proton pump inhibitors. Allergol Immunopathol (Madr). 2002;30(6):342-3.