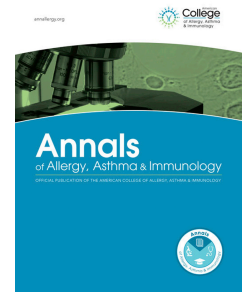


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Immediate-hypersensitivity reactions to proton pump inhibitors – experience in a medical department

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Proton pump inhibitors (PPIs) are prescribed worldwide for the treatment of acid-peptic diseases^{1,2,3}. They antagonize the enzyme H⁺/K⁺ ATPase in gastric cells, inhibiting acid secretion and raising gastric pH^{3,4}. Side effects related to PPIs are reported in only 1-3% of treated patients^{1,5}. Omeprazole, esomeprazole and pantoprazole have a similar chemical structure, differing from rabeprazole and lansoprazole^{1,5}.

According to previous studies, skin tests to PPIs are highly specific, which makes them a useful tool in diagnosing immediate hypersensitivity reactions^{1,3,5}. Previous studies about cross-reactivity (CR) between PPIs are conflicting, suggesting variable CR patterns⁶. A review of reported cases identified three CR patterns in omeprazole allergic patients: omeprazole showed CR with pantoprazole; omeprazole showed CR with pantoprazole and esomeprazole or rabeprazole but not with lansoprazole; omeprazole showed CR with all PPIs^{2,4}.

In our Allergy and Clinical Immunology Department, hypersensitivity reactions to PPIs are rare. We performed a retrospective analysis of patient's medical records from January 2014 to December 2017 and collected data from skin prick tests (SPT), intradermal tests (IDT) and drug provocation tests (DPT). Seven patients had a clinical history suggestive of an immediate-hypersensitivity reaction to PPIs (symptoms occurring ≤ 1 h after drug intake). From these patients, only 4 were selected after considering clinical history, skin test results and DPT (3 patients refused IDT and/or DPT). The youngest patient was 40 years old and the oldest 69 years old, with a mean of 51,5 years $\pm$ 12.3. In our sample, implicated PPIs were omeprazole (2), pantoprazole (1) and esomeprazole (1).

Reported symptoms were anaphylaxis (3) and urticaria (1). In those patients with anaphylaxis, suspected drugs were: omeprazole (2), pantoprazole (1). Esomeprazole was the suspected PPI in our patient with urticaria (1).

Skin tests to PPIs were performed in the volar side of the forearm, according to the European Network of Drug Allergy guidelines, using histamine (10 mg/ml) as a positive control and saline solution as a negative control⁷. SPT with pantoprazole, omeprazole and esomeprazole were performed with the commercial intravenous formulation of the drugs (40 mg/ml) and considered positive with the appearance of a ≥ 3 mm wheal 15 minutes after performing the test. IDT were performed with the intradermal injection of 0.03 ml, in dilutions 1:1000, 1:100, 1:10 and considered positive if the initial wheal increased more than 3 mm in mean diameter after 15-20 minutes.

Before starting DPT, blood pressure, heart rate, oxygen saturation, pulmonary and cardiac auscultation and cutaneous observation were evaluated/performed in every patient. DPT was performed following a single blind placebo-controlled protocol, starting with an empty capsule followed by omeprazole or esomeprazole (10mg, 10 mg, 20 mg) administered at 30-minute intervals.

Table 1 describes each patients' reaction, suspected drug, IDT results and DPT. Skin prick tests are not included in this table because there were no positive results.

One of the studied patients was a diagnostic challenge (patient 1). We briefly describe the case of a 40-year-old female patient with gastroesophageal reflux disease, referred to our consultation due to anaphylaxis (Grade 5 according to WAO⁸) to pantoprazole, occurring 30 minutes after drug intake. Due to the necessity of maintaining a PPI therapy, she was

submitted to SPT and IDT with pantoprazole, omeprazole, esomeprazole, with positive results in IDT to all PPIs tested. Despite having no intravenous formulation available in our country, we performed SPT and IDT to lansoprazole and rabeprazole, also with positive results in IDT. Skin tests with lansoprazole and rabeprazole were performed with tablets: lansoprazole 30 mg smashed and diluted in 1 ml of 0.9% NaCl; rabeprazole 20 mg smashed and diluted in 1ml of 0.9% NaCl. IDT with lansoprazole was performed in three dilutions, 1:1000, 1:100 and 1:10 (0.03, 0.3, and 3 mg/ml) as well as rabeprazole – 1: 1000, 1:100 and 1:10 (0.02, 0.2 and 2mg/ml) according to Otani & Banerji⁴. SPT and IDT to lansoprazole and rabeprazole were performed in 5 control subjects, with negative results. Considering the severity of the reaction (anaphylaxis), she was treated with ranitidine, with good tolerance to the drug and good clinical response.

In patients 2, 3 and 4, we could observe that the DPTs performed with an alternative PPI based on IDT results were negative, which points out to the fact that clinicians can rely on intradermal tests results to decide which drug to elect for a safe DPT and posterior maintenance treatment. In 3/3 patients it was possible to maintain a therapy with an alternative PPI with good clinical tolerance.

In this study we highlight the utility of IDT in diagnosing PPI immediate hypersensitivity, being essential for the identification of the suspected PPI and to the identification of a safe alternative. Furthermore, we emphasize the existence of cross-reactivity between PPIs as described in our patient with anaphylaxis to pantoprazole and positive skin tests to all PPIs. Regarding CR patterns^{2,4}, in patient 2 with omeprazole as suspected PPI and positive skin tests to omeprazole and pantoprazole, we performed a DPT with esomeprazole (negative in skin tests), with negative DPT result. Some previous reports state that omeprazole showed CR with pantoprazole and esomeprazole or rabeprazole but not with lansoprazole, or that omeprazole showed CR with all PPIs², which was not observed in this particular patient. Therefore, it seems to us that CR between these drugs remains uncertain.

To our knowledge there is only one published case report describing a case of hypersensitivity to all PPIs (in a patient with anaphylaxis to pantoprazole⁹) and one case series of 5 patients with positive skin tests to all PPIs (SPT or IDT)¹⁰. In these particular cases, it is important to perform skin tests to all PPIs available, and eventually proceed to a desensitization for a better gastric disorder treatment.

Finally, contrarily to previous studies where SPT were very useful in diagnosing PPI hypersensitivity (Ozdemir et al. describe positive SPTs in 95% of patients⁵), they were not useful in our series. Our results may have a bias due to our small population. When SPT are negative, IDT must be performed in order to identify the culprit PPI. A DPT must follow, considering IDT results.

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Patient number	Gender,age	Reported reaction	Suspected PPI	IDT results	DPT
1	F, 40	Urticaria, dyspnea, hypotension (Grade 5 anaphylaxis)	Pantoprazole	Positive to: Pantoprazole 1:10 Omeprazole 1:100 Esomeprazole 1:10 Lansoprazole 1:10 Rabeprazole 1:10	Not performed Treatment with ranitidine
2	M, 69	Urticaria, dyspnea (Grade 3 anaphylaxis)	Omeprazole	Positive to: Omeprazole 1:100 Pantoprazole 1:100 Negative to Esomeprazole	Esomeprazole - negative
3	F, 48	Laryngeal edema (Grade 4 anaphylaxis)	Omeprazole	Positive to: Omeprazole 1:100 Negative to Pantoprazole and Esomeprazole	Esomeprazole – negative
4	F, 49	Urticaria	Esomeprazole	Positive to: Esomeprazole 1:100 Pantoprazole 1:100 Negative to Omeprazole	Omeprazole – negative

Table 1: Description of patient's characteristics, reactions, suspected drug, intradermal tests (IDT) results and drug provocation tests (DPT); F-female; M-male.