

ORIGINAL ARTICLE

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Hypersensitivity to inhibitors of gastric secretion: our experience and review of the literature

Ipersensibilità a farmaci inibitori della secrezione gastrica: nostra esperienza e revisione della letteratura

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Key words

Hypersensitivity • H₂ receptor antagonists • Proton pump inhibitors

Parole chiave

Ipersensibilità • Anti-H₂ • Inibitori di pompa protonica

Summary

Inhibitor drugs of gastric secretion, such as H₂ receptor antagonists and proton pump inhibitors are associated with a low incidence of adverse reactions, but both of categories can cause hypersensitivity reaction that may be severe.

We report here the results of a retrospective study on 44 patients that referred to us for hypersensitivity to inhibitor drugs of gastric secretion during the period between January 2001 and December 2006. Thirty patients reported a reaction to proton pump inhibitors (27 to one molecule, 3 to two molecules) and 14 to H₂ receptor antagonists, all of them to ranitidine. Twelve out of 44 patients underwent challenge test for an alternative drug: 5 patients were tested for ranitidine (4 negative, 1 positive) and 7 for a proton pump inhibitors (6 negative, 1 positive). Since these drugs are used for chronic diseases and for long-term treatments, it is presumable that most of patients reporting a hypersensitivity reaction to H₂ receptor antagonists or proton pump inhibitors in our study took an alternative drug without performing a challenge test. Moreover, 3 out of 29 patients with proton pump inhibitor hypersensitivity reported reactions to two molecules of proton pump inhibitors, suggesting that a cross-reactivity between PPI molecules can exist. Therefore, in our opinion, in patients with a hypersensitivity reaction to one of these molecules, is important to perform a challenge test for an alternative drug to avoid any risk factor that may occur when patients take drug at home.

Riassunto

I farmaci inibitori della secrezione acida gastrica, comprendenti gli antagonisti dei recettori H₂ e gli inibitori di pompa protonica sono associati ad una bassa incidenza di reazioni avverse, tuttavia possono essere responsabili di manifestazioni allergiche anche severe.

Riportiamo i risultati di uno studio retrospettivo su 44 pazienti con ipersensibilità a tali farmaci nel periodo compreso tra gennaio 2001 e dicembre 2006. Trenta pazienti riferivano reazione di ipersensibilità ad inibitori di pompa protonica (27 per una sola molecola e 3 per due molecole) e 14 pazienti a recettori H₂, tutti a ranitidina. Dodici pazienti su 44 sono stati sottoposti a challenge test per farmaco alternativo: 5 per ranitidina (4 con esito negativo e 1 positivo) e 7 per inibitori di pompa protonica (6 con esito negativo ed uno positivo). Come si evince, solo un quarto circa dei pazienti ha richiesto di effettuare un challenge test per molecola alternativa. Poiché tali farmaci vengono utilizzati per patologie croniche e per cicli piuttosto lunghi, appare evidente che la maggior parte dei soggetti è ricorsa ad una molecola alternativa senza l'esecuzione di un challenge test. Inoltre, 3 dei nostri pazienti riportavano reazioni a due molecole di inibitori di pompa protonica, ciò suggerisce una possibile cross-reattività tra varie molecole di inibitori di pompa protonica. Pertanto, anche se le reazioni a queste due categorie di farmaci sembrano piuttosto rare, a nostro avviso appare opportuna l'esecuzione di un test per molecola alternativa al fine di evitare possibili reazioni anche serie che potrebbero insorgere per un fenomeno di cross-reattività tra farmaci inibitori di pompa protonica.

Introduction

Among inhibitor drugs of gastric secretion there are H₂ receptor antagonists (H₂-RA) and proton pump inhibitors (PPI). Both categories are the most common

drugs used both in hospital and in general medicine for the treatment of peptic ulcer and gastroesophageal reflux disease. Even if anti-H₂ and PPI are associated with a low incidence of adverse reactions^{1,2}, both of categories can cause a hypersensitivity reaction that may

be severe. In 1999 the Uppsala Monitoring Center database reported that the frequency of anaphylactic reactions out of all reported adverse reactions for H_2 receptor antagonists and PPI were between 0.2% and 0.7%³.

PPI are benzimidazole derivatives and all the molecules actually used are structurally and pharmacologically related⁴. The molecules today commonly employed are omeprazole, the molecule first introduced in medicine in 1980, lansoprazole, pantoprazole, rabeprazole and, the most recent esomeprazole, the S-enantiomer of omeprazole.

Until now several allergic and immunological adverse reactions by PPI are reported, most of them caused by omeprazole. The first description of anaphylaxis to omeprazole was in 1996⁵, followed by other reports until 2006⁶⁻¹¹. Pantoprazole also has shown isolated cases of anaphylaxis¹²⁻¹⁶. Some cases of anaphylaxis due to more than one molecule of PPI are reported^{3 12 17 18}. Moreover, PPIs demonstrated to have high sensitizing power¹⁹, in particular omeprazole^{19 20}, lansoprazole^{19 21} and pantoprazole¹⁹. Other cutaneous, allergic or immunological reactions to PPIs are exfoliative dermatitis^{22 23}, bullous skin reaction²⁴, erythema nodosum²⁵, pityriasis rosea-like eruption²⁶, fixed eruption²⁷, leucocytoclastic vasculitis by omeprazole²⁸, toxic epidermal necrolysis by omeprazole^{29 30} and lansoprazole³¹, erythrodermia by omeprazole^{32 33} and lansoprazole³³, lichenoid eruptions by omeprazole^{34 35}, lansoprazole and pantoprazole³⁴, DRESS syndrome by esomeprazole³⁶, discoid lupus by pantoprazole³⁷. Immunological reactions include dermatomyositis³⁸, polymyositis³⁹, autoimmune haemolytic anemia^{40 41} by omeprazole, vasculitis ANCA positive by pantoprazole⁴², thrombocytopenia by lansoprazole⁴³.

In the group of H_2 -RAs, ranitidine is the most used molecule. The other substances belonging to this category are: cimetidine, nizatidine, famotidine and roxatidine. Even if ranitidine can induce sensitization in about 50% of factory workers^{44 45}, hyper-

sensitivity reactions caused by this drug are not frequent in everyday clinical practice. The drug has been associated to urticaria^{46 47}, anaphylactic reaction⁴⁸⁻⁵³, rhinitis and asthma⁵⁴, allergic contact dermatitis^{55 56}, papular erythema-type drug eruption⁵⁷, toxic epidermal necrolysis⁵⁸, lichenoid eruptions⁵⁹, UVB photosensitivity⁶⁰ and exanthematous pustulosis⁶¹. Immunological reactions to ranitidine reported in literature are Henoch-Schönlein purpura⁶², thrombocytopenia⁶³, agranulocytosis⁶⁴, autoimmune hepatitis⁶⁵, cholestatic hepatitis with rash and hypereosinophilia⁶⁶. Rarely the other molecules of the group of H_2 receptor antagonists have shown hypersensitivity reactions: cimetidine has been associated with urticaria⁶⁷, delayed hypersensitivity^{68 69}, baboon syndrome⁷⁰, toxic epidermal necrolysis⁷¹, Lyell's syndrome⁷², erythema annulare centrifugum⁷³, xerosis and asteatotic dermatitis⁷⁴, exfoliative dermatitis⁷⁵, cytopenia⁷⁶. Famotidine has been associated with anaphylactic shock⁷⁷, contact dermatitis^{78 79}, toxic epidermal necrolysis⁸⁰, agranulocytosis⁸¹. Nizatidine has been reported as cause of urticaria⁸², anaphylaxis⁸³, leukocytoclastic vasculitis⁸⁴ and roxatidine related to erythema multiforme⁸⁵, erythrodermic eruption⁸⁶ and lichenoid eruptions^{87 88}.

Here we report the results of a retrospective study on a group of patients referred to our Operative Unit of Allergy and Clinical Immunology reporting a hypersensitivity reaction to one or more drugs belonging to the family of PPIs or H_2 -RAs that underwent challenge test for an alternative drug.

Material and methods

During the period between January 2001 and December 2006 44 patients (36 females and 8 males, with an age range between 18 and 73 years) reported well-documented hypersensitivity reactions (urticaria/angioedema, respiratory symptoms, laryngeal

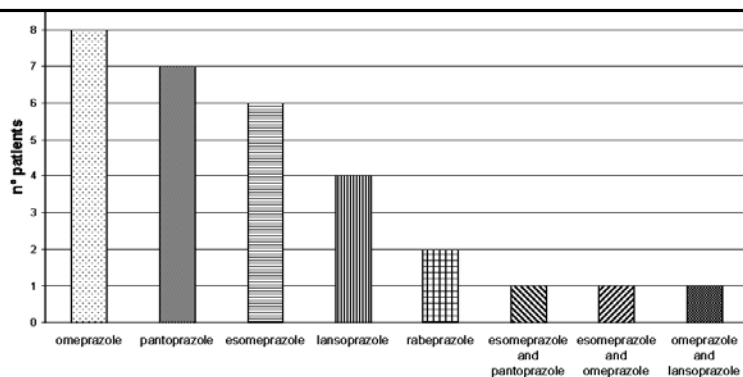


Fig. 1. Number of patients reporting hypersensitivity to one or more molecules of PPIs.

edema, anaphylaxis, exfoliative skin diseases) to inhibitor drugs of gastric secretion. Thirty patients presented a reaction to one or more PPIs, in 29 of them the reactions were reported, one patient arrived from First Aid. Fourteen patients out of 44 reported a hypersensitivity to H_2 -RAs, all of them to ranitidine. In the group of patients with PPIs hypersensitivity, 26 patients reported a reaction to one molecule only: 8 to omeprazole, 7 to pantoprazole, 6 to esomeprazole, 4 to lansoprazole, 2 to rabeprazole. Three patients reported reactions to two molecules of PPIs: 1 to esomeprazole and pantoprazole, 1 to esomeprazole and omeprazole and 1 to omeprazole and lansoprazole (Fig. 1). Twelve out of 44 patients underwent challenge test for an alternative drug: 5 patients were tested for ranitidine, 7 for a PPIs.

Results

In the group of patients tested for ranitidine, 4 tests were negative, 1 positive (Fig. 2). In detail the molecules of PPIs tested were esomeprazole in 4 patients, omeprazole in 2 patients and rabeprazole in 1 patient. Six tests were negative, 1 positive for omeprazole (Fig. 2). The challenge tests were performed during hospitalization. The two reactions were easily managed and none of them was severe.

Discussion

As these data show, only 27% of patients with a hypersensitivity reaction to an anti-secretory drug referred to us to perform a challenge test for an alternative drug. It is well known that approximately 10-18% of North American and European adults report heartburn, the cardinal feature of gastro-oesophageal reflux disease (GERD), on a daily basis, and 40% have symptoms at least once a month^{89 90}. Primary

care physicians routinely evaluate symptoms, make a clinical diagnosis of GERD and base treatment decisions on this clinical diagnosis. So the total use of anti-secretory medications (H_2 -RAs and PPIs in particular) is continuously increasing. Since GERD and the other pathologies that need anti-secretory treatment, such as gastric ulcer, duodenal ulcer, Barrett's oesophagus, and helicobacter pylori infection, are chronic diseases, usually they require a long-term therapy. For instance, three-quarters of the GERD population report long-term treatment with a PPI⁹¹. So it is presumable that most of patients reporting a hypersensitivity reaction to H_2 -RAs or PPIs in our study took an alternative drug without performing a challenge test. However, these patients referred to us to undergo challenge test for a drug belonging to a different category, in particular antibiotics, non steroidal anti-inflammatory drugs or local anaesthetics. Moreover, 3 out of 29 patients with PPI hypersensitivity reported reactions to two molecules of PPIs, suggesting that a cross-reactivity between PPI molecules can exist. Other previous articles supported this hypothesis: Natsch et al., reported a case of urticaria to omeprazole followed by an anaphylaxis to

Fig. 3. Basic structural framework of PPIs.

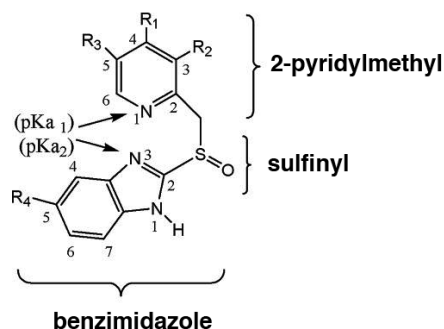


Fig. 4. Chemical structure of the 5 PPIs.

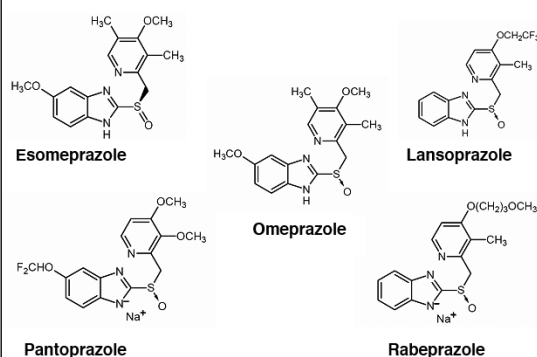
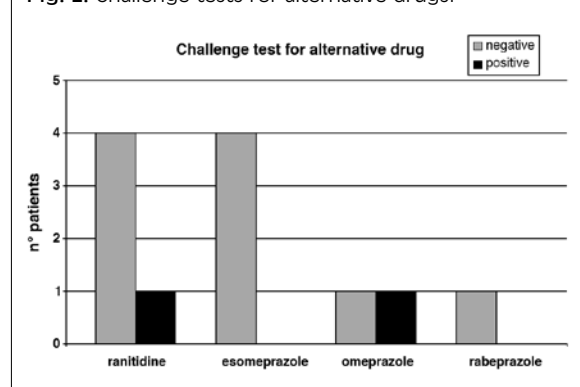


Fig. 2. Challenge tests for alternative drugs.



lansoprazole³; skin tests were not performed. Galindo et al., demonstrated by skin tests a cross-reactivity between omeprazole and lansoprazole⁶ and two other studies reported a skin prick test or an intradermal reaction positive to omeprazole, pantoprazole and lansoprazole in two patients with adverse reactions to omeprazole and lansoprazole^{17,92}. Moreover, Gonzalez et al., found elevated serum tryptase level after the adverse reaction to lansoprazole¹⁷. These reports suggest that an IgE-mediated mechanism is involved, but no specific IgE antibodies against PPIs were detected, maybe because an experimental protocol was used¹⁷. The PPI basic structural framework, is 2-pyridylmethylsulfinylbenzimidazole (Fig. 3). All the 5 PPI products currently on the market contain this pharmacophore and differ only in the nature of substituents placed on the pyridine and benzimidazole rings (Fig. 4)⁹³. Therefore, the similitude in the chemical

structure may explain the cross-reactivity between PPI molecules. Moreover, despite a cross-reaction between imidazoles has been found in dermatological field⁹⁴, a cross-reactivity between PPIs and other imidazoles (cimetidine, ketoconazole, metronidazole) has not been found¹⁷. A cross-reactivity has also been reported for ranitidine and other H₂-RAs, as cimetidine⁹⁵ and nizatidine⁹⁶.

In conclusion, both the categories of drugs, PPIs and H₂-RAs, are usually well tolerated. However, our reports and the findings of literature suggest that these drugs may represent a life threatening risk. Moreover, the possibility of cross-reactions in both the groups of drugs, should be taken in account; therefore, in our opinion, in patients with a hypersensitivity reaction to one of these molecules, is important to perform a challenge test for an alternative drug to avoid any risk factors that may occur when the patients take drug at home.

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