

Hypersensitivity reactions to proton pump inhibitors in childhood

Francesca Mori¹  | Fabrizio Franceschini²  | Francesca Saretta³  |
Annamaria Bianchi⁴  | Paolo Bottau⁵ | Silvia Caimmi⁶  | Giuseppe Crisafulli⁷ |
Lucia Liotti⁸  | Claudia Paglialunga⁹ | Carlo Caffarelli¹⁰ 

¹Allergy Unit, Department of Pediatrics, Meyer Children's University Hospital, Florence, Italy

²UOC Pediatria, Azienda Ospedaliero-Universitaria "Ospedali Riuniti", Ancona, Italy

³SC Pediatria, Ospedale Latisana-Palmanova, Dipartimento Materno-Infantile Azienda Sanitaria, Universitaria Friuli Centrale, Italy

⁴Pediatria, Ospedale San Camillo, Roma, Italy

⁵Pediatria e Neonatologia, Ospedale di Imola, Imola, Italy

⁶Clinica Pediatrica Policlinico San Matteo, University di Pavia, Pavia, Italy

⁷UO Allergologia, Dipartimento di Pediatria, Università di Messina, Messina, Italy

⁸Pediatria, Ospedale Principi di Piemonte, Senigallia, Italy

⁹UOC di Pediatria, Azienda Ospedaliera-Universitaria "Consortiale-Policlinico", Ospedale Pediatrico Giovanni XXIII, Bari, Italy

¹⁰Clinica Pediatrica, Dipartimento Medicina e Chirurgia, Università di Parma, Parma, Italy

Correspondence

Carlo Caffarelli, Clinica Pediatrica, Dipartimento Medicina e Chirurgia, Università di Parma, Via Gramsci 14, 43100 Parma, Italy.

Email: carlo.caffarelli@gmail.com

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Abstract

Hypersensitivity reactions (HRs) to proton pump inhibitors (PPIs) are mainly described in adults. Anyway, increased use of PPIs in childhood has been observed in recent years. In the literature, only case reports are published on children. Most of the PPI HRs are IgE-mediated. Skin test concentrations and allergy workup protocols used for adults are also applied in children. This study underlies that multicentric pediatric studies focusing on PPI reactions in children are needed.

KEYWORDS

childhood, drug hypersensitivity, proton pump inhibitors

1 | INTRODUCTION

Proton pump inhibitors (PPIs) are prescribed in children suffering from gastroesophageal reflux disease (GERD), esophagitis (both erosive and eosinophilic types), to eradicate *Helicobacter* and to prevent non-steroidal anti-inflammatory drugs (NSAIDs) and

steroid-associated gastritis. PPIs have a good safety profile, and side effects occur in 1%-3% of patients. In children, PPI gastric inhibition has been associated with a higher risk of fracture, pneumonia, toxicity in long-term use, hypersensitivity reactions (HRs) to other drugs, and food allergy development. Increased use of PPIs in childhood has been observed, but no proportional increase of immune-mediated

reaction to PPIs has been reported.¹ In particular, there is a lack of studies on the incidence and prevalence of PPI HRs, especially in children, mostly case reports or small case series.

Moreover, the underlying mechanisms of HRs to PPIs cannot be entirely explained yet. Most of the PPI HRs are IgE-mediated. An IgE-mediated mechanism has also been reported in reactions occurring after 3–24 hours from PPI intake. This may be due to the delayed-release formulation of some PPIs or polymorphisms in the cytochrome P450 CYP2C19 gene leading to slow drug metabolism. Regarding delayed reactions, type II and T cell-mediated hypersensitivity reactions have been reported as well. In general, sensitization to PPIs may occur by oral, intravenous, or skin routes.

2 | IMMEDIATE REACTIONS

In the Uppsala Monitoring Centre database of suspected adverse drug reactions (ADRs), PPIs triggered 0.8% of anaphylaxis.² In the French pharmacovigilance database, among 2119 cases of potentially relevant immediate-type HRs, PPIs elicited anaphylactic reactions in 14 patients and urticaria-angioedema in 6.³ An extensive review of case reports or small case series of HRs to PPIs¹ found that most patients [309 (69%) out of 443] had immediate HRs. Anaphylaxis occurred in 163 (53.6%) cases and urticaria and/or angioedema in 134 (44.1%).

The relative frequency of each PPI involvement seems to vary based upon local habits in PPI prescriptions.¹ All immediate HRs to PPIs are reported in adults except for a few case reports in pediatric age. A 16-year-old girl developed anaphylaxis to omeprazole and pantoprazole.⁴ Another case report of anaphylaxis to omeprazole was reported in a 14-year-old teenager.⁵ Baldassarre et al⁶ reported that an infant with severe GERD developed respiratory symptoms (and sporadic facial edema) after the administration of omeprazole or esomeprazole.

3 | DELAYED REACTIONS

T cell-mediated delayed reactions are reported in about 30% of patients with HRs to PPIs, ranging from maculopapular exanthemas to severe cutaneous adverse reactions (SCARs).¹

Cytopenia is a rare adverse event associated with PPI treatment, probably caused by toxic or immune-mediated mechanisms (type II HRs). PPIs have also been associated with photoallergic dermatitis, vasculitis, interstitial nephritis, and cutaneous lupus erythematosus. We have not found children with delayed reactions to PPIs in the literature.

4 | CROSS-REACTIVITY

Cross-reactivity among PPIs has been described both in case of immediate and delayed reactions.

Key messages

Hypersensitivity reactions to proton pump inhibitors must be bear in mind, and proton pump inhibitors should be used no more than necessary. Innovative approaches that improve diagnosis and treatment need to be developed.

There are three possible patterns of cross-reactivity described so far:

1. Pattern 1 or class effect: patients who show hypersensitivity to a single PPI (commonly omeprazole) and react to all other PPIs. This is due to the 2-pyridyl-methyl-sulfinyl-benzimidazole nucleus shared by all the PPIs.
2. Pattern 2 or cross-reactivity based on side-ring substitution homologies:
 - a. Patients with hypersensitivity to omeprazole who also reacted to lansoprazole because of the nature of substitutions in their benzimidazole ring: a methoxy chain and a difluoromethoxy chain, respectively.
 - b. Patients with hypersensitivity to lansoprazole or rabeprazole due to changes at the pyridine nucleus level with a trifluoromethoxy chain or a methoxypropoxy chain, respectively.
3. Pattern 3 or hypersensitivity to a single PPI: patients with allergy to a single PPI and tolerance of other PPIs.

However, not all cross-reactivity patterns can be explained with this classification, so several different chemical characteristics (ie, metabolites) may be involved.¹ Clinicians must be aware of the possible cross-reactivity among PPIs; for that reason, a complete allergy workup needs to be performed to find a safe alternative.

5 | HOW TO PERFORM THE DIAGNOSIS

The temporal relationship between PPI intake and onset of reaction is critical for suspecting an HR to a PPI. However, clinical history can be unclear since PPIs are frequently taken in combination with other drugs and after meals.

In IgE-mediated HRs, skin tests (STs) have high specificity and positive predictive value, and they are safe.⁷ Bonadonna et al suggested the following non-irritant concentration for STs⁷:

- Omeprazole, esomeprazole, pantoprazole, and rabeprazole at 40 mg/mL for skin prick tests (SPTs) and at 0.4 mg/mL for intradermal tests (IDTs);
- Lansoprazole (prepared by dissolving the powder in saline) at 30 mg/mL for SPT.

Otani et al proposed three dilutions at 0.04, 0.4, and 4 mg/mL for omeprazole, esomeprazole, and pantoprazole IDTs.⁸ It is

recommended to use only injectable intravenous preparations of PPI for IDTs because oral preparations can be irritating.

The basophil activation test (BAT) may improve the diagnosis of IgE-mediated allergic reactions to PPIs.⁹

In T cell-mediated HSRs to PPIs, a delayed reading of IDT at 24 and 48 hours, as well as a patch test using different drug concentrations (from 0.1% to 50% in petrolatum or saline solution), have been described, but diagnostic accuracy has not been determined.

A drug provocation test (DPT) should be performed in patients with non-anaphylactic immediate reactions when ST results are negative. As reported in several studies, during DPT, increasing doses of PPI are administered orally at 30- to 60-min intervals until therapeutic doses or symptoms appear, under strict hospital surveillance. Many authors, referring to the adult population, suggest dividing the therapeutic dose into escalating doses: 5 mg, 10 mg, and 20 mg or 5 mg, 10 mg, and 20 mg for omeprazole, pantoprazole, esomeprazole, and rabeprazole⁹; 3.25 mg, 7.5 mg, and 15 mg or 5 mg, 10 mg, and 15 mg for lansoprazole. When performing DPT in children, it is mandatory to adapt the dosage of PPI to the patient's weight. Laguna et al⁹ propose to execute a DPT in two days, administering the therapeutic dose after a gap of 24 hours. Regarding delayed reactions, a DPT can be performed when there is a history of a mild maculopapular eruption.

6 | ORAL DESENSITIZATION

Oral desensitization may be considered in patients with a confirmed, immediate reaction to PPI, when the drug is necessary, and the patient has positive skin testing to all available PPIs. This has only been reported in one patient (Table 1) with omeprazole-induced anaphylaxis.¹⁰ Oral desensitization is not appropriate for patients with delayed reactions.

7 | CONCLUSIONS

Most of the studies on HRs to PPIs focus on adults. Only a few cases have been reported in children. It can be speculated that children have a true lower incidence of HRs to PPIs (ie, a different metabolism) or that PPI HRs have not been properly investigated in children. In patients with possible IgE-mediated HRs to PPIs, STs are specific for identifying IgE-mediated HRs. ST concentrations are similar to those used for adults. In the future, multicentric pediatric studies focusing on PPI reactions in children should be proposed to find the true incidence of PPI HRs in children and properly investigate PPI reactions.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest to disclose in relation to this paper.

TABLE 1 Omeprazole desensitization protocol: Doses were increased at 20-minute intervals.¹⁰

Time	Dose (mg)	Cumulative dose (mg)
T1	0.01	0.001
T2	0.002	0.003
T3	0.004	0.007
T4	0.008	0.015
T5	0.01	0.025
T6	0.02	0.045
T7	0.04	0.085
T8	0.08	0.165
T9	0.1	0.265
T10	0.2	0.465
T11	0.4	0.865
T12	0.8	1.665
T13	1	2.665
T14	2	4.665
T15	4	8.665
T16	8	16.665
T17	16	32.665

AUTHOR CONTRIBUTIONS

Francesca Mori: Conceptualization (equal); Data curation (equal); Writing-original draft (equal); Writing-review & editing (equal). **Fabrizio Franceschini:** Data curation (equal); Visualization (equal); Writing-original draft (equal); Writing-review & editing (equal). **Francesca Saretta:** Data curation (equal); Visualization (equal); Writing-original draft (equal); Writing-review & editing (equal). **Annamaria Bianchi:** Data curation (equal); Writing-original draft (equal); Writing-review & editing (equal). **Paolo Bottau:** Data curation (equal); Writing-original draft (equal); Writing-review & editing (equal). **Silvia Caimmi:** Data curation (equal); Writing-original draft (equal); Writing-review & editing (equal). **Giuseppe Crisafulli:** Data curation (equal); Writing-original draft (equal); Writing-review & editing (equal). **Lucia Liotti:** Data curation (equal); Writing-original draft (equal); Writing-review & editing (equal). **Claudia Paglialunga:** Data curation (equal); Writing-original draft (equal); Writing-review & editing (equal). **Carlo Caffarelli:** Conceptualization (equal); Supervision (equal); Writing-original draft (equal); Writing-review & editing (equal).

ORCID

Francesca Mori  <https://orcid.org/0000-0001-7483-0128>
 Fabrizio Franceschini  <https://orcid.org/0000-0003-1494-9113>
 Francesca Saretta  <https://orcid.org/0000-0001-9443-5483>
 Annamaria Bianchi  <https://orcid.org/0000-0001-8896-3597>
 Silvia Caimmi  <https://orcid.org/0000-0003-0515-524X>
 Lucia Liotti  <https://orcid.org/0000-0002-5699-2796>
 Carlo Caffarelli  <https://orcid.org/0000-0001-7710-6995>

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