



Antihistamines: ABC for the pediatricians

Giuseppe Fabio Parisi¹ | Amelia Licari² | Maria Papale¹ | Sara Manti^{1,3} | Carmelo Salpietro³ | Gian Luigi Marseglia² | Salvatore Leonardi¹

¹Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy

²Department of Pediatrics, Foundation IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy

³Department of Pediatrics, Unit of Pediatric Genetics and Immunology, University of Messina, Messina, Italy

Correspondence

Giuseppe Fabio Parisi, Department of Clinical and Experimental Medicine, University of Catania, Via Santa Sofia, 78 - 95123 Catania, Italy.
Email: giuseppeparisi88@hotmail.it

Abstract

Antihistamines are currently one of the most commonly administered drugs in children. They are used to treat symptoms that depend on histamine release, namely allergic diseases, such as rhinitis, asthma, urticaria, and anaphylaxis. It is possible to distinguish first- and second-generation antihistamines. Pharmacological effects and therapeutic indications are similar, but second-generation antihistamines have fewer adverse effects because they are more selective for peripheral H1 receptors. Although they have been on the market for several years, there are still many adverse effects linked to the antihistamine safety profile, especially in the first years of life. Thus, many antihistamines are prescribed off-label, especially in children younger than 2 years of age, which is the age-group where most of the data on drug safety are lacking and many antihistamines are not recommended. This article aims to provide a practical update on the use of antihistamines in children.

KEYWORDS

antihistamines, children, H1 receptors, histamine, pediatrician

1 | INTRODUCTION

Histamine is one of the most important mediators of allergy, inflammation, anaphylaxis, and gastric acid secretion. The concentration of histamine is particularly high in tissues that contain many mast cells, such as the respiratory tree, intestinal mucosa, and skin. Histamine can act on four types of receptors: H1, H2, H3, and H4. H1 and H2 receptors are distributed in both the peripheral and the central nervous system (CNS) and allow histamine to exert effects on smooth muscles and mucous glands. By acting on H1, histamine causes itching, stimulates secretion from the nasal mucosa, contracts smooth muscle in the bronchi and intestines, and relaxes smooth muscle in small blood vessels. Additionally, histamine stimulates gastric acid secretion via H2 receptors. H3 receptors are mainly expressed in the CNS and act as autoreceptors on histaminergic neurons, inhibiting the release of histamine and modulating other neurotransmitters. H4 receptors are found on cells of the immune system, in the

gastrointestinal tract, in the CNS, and on afferent neurons with primary sensors. The action of histamine on H4 receptors induces chemotaxis, cytokine secretion, and upregulation of adhesion molecules.¹

H1 antihistamines are widely used in pediatric patients to treat histamine-dependent symptoms. It is possible to distinguish first- and second-generation antihistamines; pharmacological effects and therapeutic applications are similar, but second-generation antihistamines have fewer adverse effects because they are more selective for peripheral H1 receptors.¹ Some second-generation antihistamines have also some important additional anti-inflammatory effects that occur by a decrease in production of cytokines and release of other mediators by mastocytes and basophils; in recruitment of eosinophils in the late phase of allergic reactions; and in expression of membrane receptors in nasal epithelial cells and vascular endothelium, mainly concerning the adhesion molecule ICAM-1, which favors leukocyte migration from the blood to the respiratory

mucosa and constitutes the main receptor for rhinovirus implicated in asthma exacerbation.²

2 | SAFETY ISSUE

Antihistamines are widely prescribed in children.³ Although they have been on the market for several years, there are still many adverse effects, especially in the first years of life. In clinical practice, antihistamines are commonly prescribed off-label, especially in children younger than 2 years of age: In this age, there is a lack of data on drug safety and many antihistamines are not recommended.³

Antihistamines, especially first-generation antihistamines, have central effects that cause drowsiness, tiredness, increased appetite, or worsening of cognitive functions. They also have antimuscarinic, antiadrenergic, and antiserotonergic activity, which may cause vision disorders, dry mouth, tachycardia, and confusion.^{3,4} Some antihistamines, particularly ebastine and mizolastine, can cause a significant prolongation of the QT interval on electrocardiogram, which can cause also severe, even fatal, arrhythmias. It may occur when other drugs, interfering with cytochrome P450, are contemporarily administered, for example, macrolides and antifungals.^{3,4}

3 | INDICATIONS IN CHILDREN

The main indication of antihistamines is the relief of allergic symptoms, which depend on histamine release, such as itching, sneezing, rhinorrhoea, and congestion. Second-generation anti-H1 molecules with little or no sedative effect are preferred.⁴ Church et al⁵ demonstrated that treatment with second-generation anti-H1 antihistamines in children with allergic rhinitis did not lead to a reduction in school performance. The main route of administration is oral, while the parenteral route, which is only possible with some first-generation molecules, is reserved for the prevention or treatment of serious and rare events (episodes of anaphylaxis, blood transfusions, and adverse drug reactions). The topical route is reserved for ophthalmic, nasal, or cutaneous disease (eye drops, nasal spray, cream, and gel).⁴

First-generation antihistamines are considered safe to use during pregnancy. There are relatively fewer data on the non-sedating second-generation antihistamines; however, published studies are reassuring. All antihistamines are considered safe to use during breastfeeding, as minimal amounts are excreted in the breast milk and would not cause any adverse effects on a breastfeeding infant.⁶

3.1 | Allergic rhinoconjunctivitis

Histamine is the most powerful mediator that is released during the early phase of the allergic reaction, and this is the cause of itching, sneezing, and rhinorrhoea. The late phase, occurring 4-24 hours

Key Message

Antihistamines are currently one of the most commonly administered drugs in children. This article aims to provide a practical update on the use of antihistamines in children.

after allergen exposure, is characterized by inflammation and nasal obstruction that are more sensitive to nasal corticosteroids.⁷

The Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines recommend second-generation antihistamines for both intermittent and persistent rhinitis.⁸

3.2 | Urticaria

Anti-H1 antihistamines are effective at reducing itchiness number, size, and duration of skin manifestations in patients with both acute and chronic urticaria. The current guidelines recommend the use of second-generation molecules for their tolerability and safety profile, which allows their use and dose to be modulated over time. In chronic urticaria, guidelines suggest to progressively increase the dose of second-generation H1 antihistamines up to fourfold higher than the standard dose, when there is treatment failure.⁹

3.3 | Atopic dermatitis

The use of anti-H1 antihistamines in the management of atopic dermatitis remains controversial. Itching resulting from dermatitis recognizes a complex pathogenesis that does not result from histamine release alone, but there is also the involvement of several other mediators that can cause itching. The National Institute for Health and Care Excellence (NICE) guidelines for treating atopic eczema suggest a 1-month trial of a non-sedating antihistamine in children with severe itching; this treatment should be reviewed every 3 months.¹⁰

3.4 | Anaphylaxis

Intramuscular adrenaline is the lifesaving medication in anaphylaxis. As part of the international guidelines for anaphylaxis management, intravenous antihistamine administration is part of the emergency interventions together with adrenaline and corticosteroids.¹¹ However, oral antihistamines can help to control mild anaphylactic reaction. Among emergency department patients with allergic reactions, anti-H1 administration was associated with a lower likelihood of progression to anaphylaxis. These data indicate that early treatment in the pre-hospital setting may decrease progression to anaphylaxis

3.5 | Asthma

Mast cells play a critical role in the pathogenesis of allergic asthma. Histamine plays a role in airway obstruction via smooth muscle contraction, bronchial secretion, and airway mucosal edema. However, previous clinical trials with antihistamines in the asthma treatment were not successful. This happens because asthma is an extremely complex disease that involves more than just histamine as a pathogenic mediator.¹² However, antihistamines may have a role in patients with allergic asthma and rhinitis. Combined treatment using nasal corticosteroids and antihistamines in children with allergic rhinitis has been shown to significantly improve asthma symptoms. Thus, therapy with anti-H1 antihistamines confers an additional benefit in the control of asthmatic symptoms in asthmatics with concomitant allergic rhinitis.¹³

3.6 | Other diseases

There is no evidence for the efficacy of H1 antihistamines that are used to treat otitis media, common cold, and non-specific cough.⁴ However, antihistamines may be trialed in children with allergic cough.¹⁴

In conclusion, H1 antihistamines are frequently used in pediatric patients to treat many allergic diseases according to evidence-based medicine while in other cases an off-label use was made with contradictory results. The effectiveness of second-generation antihistamines has been well studied, and they should be preferred to decrease adverse effects.

ORCID

Giuseppe Fabio Parisi  <https://orcid.org/0000-0003-4291-0195>

Amelia Licari  <https://orcid.org/0000-0002-1773-6482>

Sara Manti  <https://orcid.org/0000-0001-5420-8411>

Gian Luigi Marseglia  <https://orcid.org/0000-0003-3662-0159>

REFERENCES

1. Tatarkiewicz J, Rzedkiewicz P, Żochowska M, Staniszevska A, Bujalska-Zadrożny M. New antihistamines - perspectives in the treatment of some allergic and inflammatory disorders. *Arch Med Sci.* 2019;15(2):537-553.
2. Ritchie AI, Farne HA, Singanayagam A, et al. Pathogenesis of viral infection in exacerbations of airway disease. *Ann Am Thorac Soc.* 2015;12(Suppl. 2):S115-S132.
3. Motola D, Donati M, Biagi C, et al. Safety profile of H1-antihistamines in pediatrics: an analysis based on data from VigiBase. *Pharmacoepidemiol Drug Saf.* 2017;26(10):1164-1171.
4. Fitzsimons R, van der Poel LA, Thornhill W, du Toit G, Shah N, Brough HA. Antihistamine use in children. *Arch Dis Child Educ Pract Ed.* 2015;100(3):122-131.
5. Church MK, Maurer M, Simons FE, et al. Risk of first-generation H(1)-antihistamines: a GA(2)LEN position paper. *Allergy.* 2010;65:459-466.
6. So M, Bozzo P, Inoue M, Einarson A. Safety of antihistamines during pregnancy and lactation. *Can Fam Physician.* 2010;56(5):427-429.
7. Licari A, Ciprandi G, Marseglia A, et al. Current recommendations and emerging options for the treatment of allergic rhinitis. *Expert Rev Clin Immunol.* 2014;10:1337-1347.
8. Brożek JL, Bousquet J, Agache I, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. *J Allergy Clin Immunol.* 2017;140(4):950-958.
9. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA2LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria. The 2017 revision and update. *Allergy.* 2018;73(7):1393-1414.
10. National Institute for Health and Clinical Excellence. Atopic eczema in children: management of atopic eczema in children from birth up to the age of 12 years. 2007. <http://www.nice.org.uk/guidance/CG57>. Accessed April 23, 2019.
11. Muraro A, Roberts G, Worm M, et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. *Allergy.* 2014;69(8):1026-1045.
12. Yamauchi K, Ogasawara M. The Role of Histamine in the Pathophysiology of Asthma and the Clinical Efficacy of Antihistamines in Asthma Therapy. *Int J Mol Sci.* 2019;20:1733.
13. Licari A, Castagnoli R, Denicolò CF, Rossini L, Marseglia A, Marseglia GL. The Nose and the Lung: United Airway Disease? *Front Pediatr.* 2017;3(5):44.
14. Chang AB, Peake J, McElrea MS. Anti-histamines for prolonged non-specific cough in children. Update of Cochrane Database Syst Rev 2006;(3):CD005604; PMID: 16856107. *Cochrane Database Syst Rev.* 2008 (2):CD005604.

How to cite this article: Parisi GF, Licari A, Papale M, et al. Antihistamines: ABC for the pediatricians. *Pediatr Allergy Immunol.* 2020;31(Suppl 24):34-36. <https://doi.org/10.1111/pai.13152>