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Review article

Antihistamines in pediatric allergy

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Abstract
Histamine is a key mediator in allergic diseases, where it exerts most of its effects through the H1 receptor and to a less extent the H2 receptor. H1-antihistamines provide rapid relief of many of the allergic symptoms and are considered the main stay of treatment of allergic rhinoconjunctivitis and urticaria. H1 antihistamines comprise first generation (old) and second generation (new) H 1 antihistamines with different pharmacological aspects, efficacy and safety profile. Few studies dealt with H1 antihistamines in pediatric population. This review will highlight the characteristics of H1 antihistamines and their indications in pediatric allergic disorders.

Allergic diseases constitute the most common causes of chronic illness in developed countries and the incidence rising in developing countries. It has been proposed that there is a worldwide epidemic of allergic diseases which is likely to be a consequence of the changing environment and improved general health, superimposed on a range of genetic susceptibilities. Therefore, the treatment of allergy should have high priority in most countries.[1]

Histamine (one of the key mediators released from mast cells and basophils), plays a major role in the pathophysiology of allergic diseases, including rhinitis, urticaria, asthma and anaphylaxis.[2] The effects of histamine are exerted through three well defined classical G protein coupled histamine receptor (HR) subtypes termed H1R, H2R, and H3R[3] and the more recently described H4R.[4] There is also a fifth category including ill-defined histamine receptors such as an intracellular receptor labelled Hic. Its existence has so far only been inferred by the presence of small amounts of histamine in cells not traditionally thought to contain histamine[5]. All have constitutive activity, which is defined as the ability to trigger downstream events even in the absence of ligand binding.[6]

Histamine signalling through H1R is responsible for the majority of the immediate manifestations of allergic disease namely pruritus, pain, vasodilatation, vascular permeability, hypotension, flushing, headache, tachycardia, bronchoconstriction, and stimulation of airway vagal afferent nerves and cough receptors as well as decreased atrioventricular-node conduction. However, certain effects such as hypotension, tachycardia, flushing, headache, itching and nasal congestion are mediated through both H1 and H2 receptors.[2,7]

Considering all the above roles of histamine on H1 receptors, it is clear that anti-H1antihistamines are the most common drugs used to treat allergic diseases.[8] H1 antihistamines are not receptor antagonists as previously thought, but are inverse agonists.[9] When neither histamine nor antihistamine is present, the active and inactive states of the H1 receptor are in equilibrium or a balanced state. Histamine combines preferentially with the active form of the receptor to stabilise it and shift the balance towards the activated state and stimulate the cell[10]. Antihistamines stabilise the inactive form and shift the equilibrium in the opposite direction. H1 antihistamines reduce the expression of pro-inflammatory cell adhesion molecules and the accumulation of inflammatory cells, such as eosinophils and neutrophils. Major clinical effects of H1 antihistamines are seen in suppression of the early response to allergen challenge in the conjunctiva, nose, lower airway and skin.[2]

The anti-inflammatory effects of H1 antihistamines are exerted through receptor-dependent and -independent mechanisms. Receptor-dependent mechanisms involve the stabilization of the histamine receptor in its inactive conformation. A possible site where they could exert an anti-inflammatory activity is at the level of the transcription factors, NF-kB and GATA3. This would lead to inhibition of these factors dependent cytokines and adhesion molecules.[8]

Receptor-independent effects consist of inhibition of inflammatory cell activation including the de novo generation of proinflammatory products such as superoxide radicals, and the arachidonic acid products LTB4 and LTC4, and the release of granule associated products, such as neutrophil elastase and

eosinophil cationic protein. The suggested mechanisms include the inhibition of calcium mobilization and of the activity of membrane-associated enzymes such as inhibition of protein kinase C and NADPH oxidase. However, these actions require high drug concentrations, not corresponding to therapeutic dosages.[8]

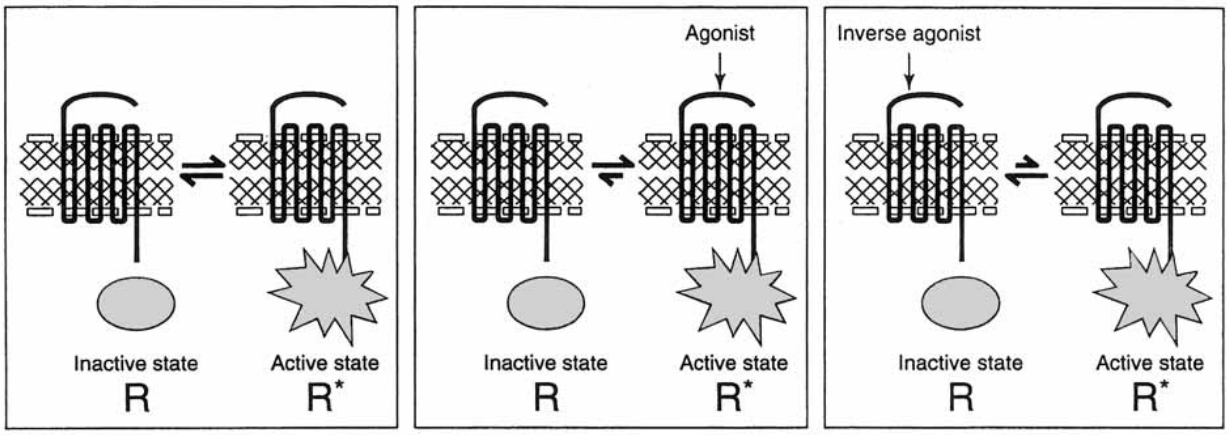

Figure 1. Simplified two-state compartment model of the histamine H1-receptor (Quoted from Leurs et al, 2002)[10]

Classification of H1 antihistamines

H1 antihistamines are classified into the *older, or first generation antihistamines*, and the *newer or second generation antihistamines*. The main differences between the two generations of drugs are their propensity to cause central nervous system side effects.[2]

The *first-generation H1 antihistamines* such as diphenhydramine, chlorpheniramine, clemastine, triprolidine, cyproheptadine, brompheniramine and hydroxyzine are highly lipophilic and hence they penetrate well into the CNS where they induce sedation. Furthermore, first-generation antihistamines are very receptor non-selective, often exhibiting high affinity for dopaminergic, serotonergic, alpha-adrenergic, and cholinergic receptors in the brain.[11,12]

The *second-generation H1 antihistamines* were first developed in the early 1980s to improve on the sedative and anticholinergic adverse effects. However, two of these, astemizole and terfenadine, have serious cardiac side effects, resulting in prolonged Q-T intervals and arrhythmias and were withdrawn from the market. The currently available second-generation antihistamines include cetirizine, loratidine, desloratadine, fexofenadine, acrivastine, azelastine, and levocetirizine.[11,13,14] The second generation antihistamines have improved H1 – receptor selectivity, absence or decreased sedation, faster onset and longer duration of action and fewer adverse effects.[15]

Pharmacokinetics and dynamics of H1 antihistamines

The drug pharmacokinetic and pharmacodynamic characteristics can differ greatly depending on the age group considered. These characteristics determine efficacy and particularly safety, and make it possible to predict the behavior of a given drug in the body. In general, antihistamines are well absorbed following oral administration as both solid and liquid formulations, and reach maximum plasma concentrations between 1-4 hours after dosing in both children and adults.[16]

The bioavailability of fexofenadine may be altered by simultaneous consumption of grapefruit juice (reduced rate of absorption of the drug by almost 30%). However, grapefruit juice does not affect the absorption of other second-generation antihistamines.[17] Although topical intranasal and ophthalmic H1 antihistamines differ in their pharmacokinetics, most of the topical preparations need to be

administered twice daily because of the washout from the nasal mucosa or conjunctiva.[2]

Most antihistamines are metabolized and detoxified within the liver by the group of enzymes belonging to the P450 cytochrome system. Only acrivastine, cetirizine, levocetirizine, desloratadine and fexofenadine avoid this metabolic passage through the liver to an important degree which makes them more predictable in terms of their desirable and undesirable effects. Cetirizine and levocetirizine are eliminated in urine, mainly in unaltered form, while fexofenadine is eliminated in stools following excretion by the biliary tract, without metabolic changes. The rest of antihistamines undergo liver transformation to metabolites that may or may not be active, and whose concentrations in plasma depend on the activity of the P450 enzyme system.[18,19]

The plasma half-life depends on the drug metabolization and clearance processes within the body, and although such processes are the same in both children and in adults, they are comparatively accelerated in children in the case of certain antihistamines. As a result, ideal dosing in such cases is once every 12 hours instead of once every 24 hours (e.g., in the case of levocetirizine in kindergarten children).[20-22] The activity of the liver enzyme complex can also be altered under special metabolic conditions such as infancy, advanced age, liver diseases or by direct drug action upon the enzyme complex.[23-26]

Drug interactions resulting in a decrease in plasma concentration of the drug may lessen its clinical efficacy, as occurs when administering H1 antihistamines together with cytochrome P450 inducers such as the benzodiazepines.[27] In other cases an increase in plasma concentration of the antihistamine can result, and its adverse effects may thus increase as well. This occurs when coadministering the drug with other P450 cytochrome substrates that competitively inhibit its metabolism, such as the macrolides, antifungals or calcium antagonists.[28] In these cases the safety margin of the antihistamine, i.e., the concentration range for which the incidence of adverse events is minimal, will be a very important consideration, since the plasma levels will be unpredictable. Thus, drug dose adjustment may prove necessary in all the above mentioned situations.[18]

There are no studies of the effects of possible drug interactions in the pediatric age group between antihistamines and P450 cytochrome inhibitors, or drugs which are metabolized via this pathway. The only exception is a study of children with chloroquine-resistant malaria, where the plasma concentrations of this drug were seen to be significantly greater, and were reached sooner, when administered in combination with chlorpheniramine.[29]

The pharmacodynamic aspects, such as the onset of action and its duration, are studied both in children and in adults based on the histamine-induced skin wheal and erythema inhibition model. In the same way as in adults, no tachyphylaxis or tolerance of this effect on histamine-induced wheal and erythema production is observed.[30]

Adverse effects of H1 antihistamines

The different national and international drug agencies admit that there are currently many medicines authorized for use in children that have never been adequately investigated for application in such patients although in their day they received authorization out of a lack of regulation of the required specifications. In this sense, their use is still allowed because the pharmacovigilance systems have not detected any adverse effects requiring their withdrawal from the market.[16]

First-generation antihistamines have the greatest serious adverse effects. There are no long-term safety studies on the first-generation antihistamines. These older antihistamines have potential for serious adverse effects such as CNS depression and cardiotoxicity, and have also been associated with fatalities in accidental and intentional paediatric overdose.[31-33]

Central nervous system toxicity

In a study of 24 children diagnosed with allergic rhinitis whose ages ranged between 7 and 14 years of age, both chlorpheniramine and cetirizine induced significant cognitive alterations versus placebo, though such

alterations were not correlated to subjective appraisal of dysfunction as assessed by means of a visual analogue scale.[34]

Multiple studies among adults have evaluated the effects that second-generation antihistamines have on the CNS. Loratadine and desloratadine were found to be comparable with placebo at therapeutic doses, but caused sedation when used off label at higher than recommended doses. In contrast, fexofenadine has been found to be free of sedative effects even at higher than therapeutic doses. Memory, attention and tracking performance were unaffected after administration of levocetirizine compared with diphenhydramine and placebo.[35-37]

An important point arising from antihistamine action upon the CNS is how such actions can affect school performance. A clinical study comparing loratadine and diphenhydramine concluded that loratadine improved academic performance, in contrast to diphenhydramine, which worsened it. Another study evaluated the impact of long-term cetirizine treatment in children with atopic dermatitis-concluding that there were no adverse effects upon learning.[38, 39]

There have been reports of many rare adverse effects in children administered first-generation antihistamines, including spasms, seizures, aggression, respiratory distress, fixed skin rash, central anticholinergic syndrome, and toxic encephalopathy in patients with skin syndromes (atopic dermatitis, varicella) involving damage to the skin barrier, in which first-generation antihistamines were applied topically.[39-47]

Cardiotoxicity

Cardiac toxic effects induced by H1-antihistamines occur rarely and independently of the H1- receptor and are not a class effect. First-generation H1-antihistamines have antimuscarinic and *a*-adrenergic blockade activity and may cause dose-related prolongation of the QT interval.[31,35]

The absence of cardiotoxicity with antihistamines such as cetirizine, loratadine, fexofenadine and ebastine has been well established. Since they have been marketed only recently, both levocetirizine and desloratadine have been required to document the absence of such cardiotoxicity according to very strict criteria, based on the new demands of the international drug agencies, in order to be authorized for use in pediatric patients, though no published studies are available.[48-50,16]

Clinical uses of H1-antihistamines in paediatric allergy

H1 antihistamines currently constitute the largest class of medications used in the treatment of allergic disorder, the dosages and formulations of some of the second generation H1 antihistamines are displayed in table 1.[2]

- ***Allergic rhinoconjunctivitis***

Allergic rhinitis (hay fever) is the most frequent chronic disorder in the pediatric population, and its prevalence is increasing. Although it is not life-threatening, it can have a significantly detrimental effect on a child's quality of life, and it may exacerbate a number of common co-morbidities, including asthma, sinusitis and seromucosal otitis.[51-53] In Alergológica-2005 Study, 44.7% of children, below the age of 14 years, with atopy had allergic rhinitis and 61% of them had conjunctivitis but only 5% presented with conjunctivitis alone.[54]

The use of H1-antihistamines is important for the treatment of allergic rhinitis in children, as many young children particularly prefer an oral medication to an intranasal medication.[55] In the same way as in adults, antihistamines are effective in alleviating most of the symptoms of pediatric allergic rhinitis: itching, rhinorrhea, and sneezing, though they appear to be less effective against nasal congestion. There are no randomized, controlled and masked clinical trials warranting the use of formulations that mix first generation antihistamines with nasal decongesting agents (systemic vaso-constrictors), despite the fact that they are so often used in paediatric practice.[16]

Regular daily administration is associated with a significant decrease in symptoms and nasal mucosal inflammation compared with 'as needed' or 'on demand' use.[56] H1-antihistamines provide relief of allergic rhinitis comparable to that provided by intranasal

cromolyn sodium 4% and are generally found to be less potent than intranasal corticosteroids in the treatment of allergic rhinitis symptoms. Leukotriene receptor antagonists (LRAs) may also be effective in certain patients with allergic rhinitis if combined with an antihistamine.[2] While many second-generation H1-antihistamines are effective and safe in the treatment of allergic rhinitis in children, only cetirizine, levocetirizine and loratadine have been studied for long-term efficacy and safety in children.[57-59] The use of intranasal H1-antihistamines like levocabastine and azelastine has the benefits of rapid onset of action and few adverse effects. These drugs are useful in children with symptoms limited to the nose or the eyes.[60-62]

In allergic conjunctivitis, the ocular symptoms induced by allergen, such as itching, tearing and reddening are reduced by administration of H1 antihistamines either systemically or topically as eye drops such as azelastine, ketotifen, levocabastine and olopatadine. Topical application usually results in faster onset of action within 5 minutes than oral administration.[63] Emedastine and levocabastine in ophthalmological solution have been shown to alleviate the symptoms of allergic conjunctivitis in children; symptoms reduction being significantly greater with emedastine than with levocabastine.[64]

- ***Childhood asthma***

A recent epidemiological study conducted in Spain, Alergológica 2005,[65] showed that in children less than 14 years of age with bronchial asthma, antihistamine treatment was indicated in up to 30% of cases. In many cases, asthmatic patients with rhinitis receive antihistamine treatment, and it has been seen that in such situations patient lung function improves significantly.[66] Likewise; scientific evidence indicates that correct management of rhinitis is associated with a significant reduction in the risk of hospital admission and/or emergency care due to asthma attacks[67].

Antihistamines such as ketotifen, cetirizine and loratadine have shown a range of effects upon asthma: they reduce exercise-induced asthma attacks,[68] improve cough in children with pollen allergy during the pollen season,[69] and improve asthma symptoms in children.[70]

The improved specificity, tolerability, and safety profile of the second-generation H1-antagonists associated with anti-inflammatory activities and bronchodilator activities, may contribute to relieve the symptoms of the upper and lower airways in patients with coexistent mild seasonal asthma and allergic rhinitis. Considering the global rise in the prevalence of allergy and asthma, the suggestion that H1-antagonists may delay the onset of asthma in infants is of considerable interest and merits further assessment.[71]

Antihistamines should never be used as monotherapy for asthma but there is evidence that these drugs give a measure of protection in histamine-induced bronchoconstriction. It is of interest to note that cetirizine provides a primary pharmacological intervention strategy to prevent the development of asthma in specifically-sensitized high risk groups of infants. Moreover, the documented anti-inflammatory activities of antihistamines may provide a novel mechanism of action for the therapeutic control of virus-induced asthma exacerbations by inhibiting the expression of intercellular adhesion molecule-1 (ICAM-1) by airway epithelial cells.[72]

- ***Atopic dermatitis***

In atopic dermatitis (AD), itching is one of the major symptoms and the resultant scratching usually causes worsening of the lesion. H1 antihistamines may relieve itching and reduce scratching. Relief of itching by H1 antihistamines is often incomplete in AD, because the itching produced by mediators other than histamine is not down-regulated.[2]

H1 antihistamines appear to relieve itching mainly through their CNS effects and thus first-generation H1 antihistamines (sedating) such as hydroxyzine and diphenhydramine are more effective for relief of itching in this disorder than are the second-generation H1 antihistamines (non-sedating).[73] The Alergológica 2005 epidemiological study showed that 73.6% of the children diagnosed with atopic dermatitis and included in the study were prescribed antihistamine therapy -a first-

generation drug being involved in 20% of the cases.[65]

However, studies have shown that second-generation medications such as cetirizine and loratadine may also relieve itching in AD.[74,75] Cetrizine was found to reduce the duration and amount of topical corticoid treatment used in children with the worst atopic dermatitis.[75]

- ***Acute and chronic urticaria***

H1 antihistamines are first-line medications in acute and chronic urticaria and very effective in providing symptomatic relief. The evidence base for the use of H1 antihistamines in acute urticaria remains small; however, recently, in a prospective, randomised, double blind, placebo-controlled, 24-month-long study, high risk children given cetirizine had significantly fewer episodes of acute urticaria than did those given placebo.[2,76]

The second-generation H1 antihistamines (non-sedating) are the only drugs with class 1 evidence and grade A recommendation.[77,78] They offer good to moderate response in 44-91% of all types of urticaria, and in 55% of patients with chronic urticaria. While the first-generation H1 antihistamines (sedating) should be reserved for those patients not controlled with second-generation antihistamines, particularly when the symptoms interfere with sleep at night.[79]

For the indication of chronic urticaria, only cetirizine, loratadine and desloratadine are approved for treatments in patients up to 2 years of age, while ebastine and levocetirizine are only contemplated in the corresponding Summaries of Product Characteristics for urticaria in children over 6 years of age.[80] Night-time sedation with hydroxyzine, combined with the day-time use of a non-sedating antihistamine such as cetirizine, fexofenadine, levocetirizine or desloratadine, is effective and safe for both adults and children.[14]

- ***Anaphylaxis***

In anaphylaxis, H1-antihistamines relieve itching, flushing, urticaria, angioedema, and nasal and eye symptoms;[81] however, they should not be substituted for epinephrine because they are not life-saving; that is, they do not prevent or relieve upper airway obstruction, hypotension, or shock.[82-84]

Because first-generation H1 antihistamines such as chlorpheniramine, diphenhydramine, and hydroxyzine have high aqueous solubility and are available in parenteral formulations for injection, they continue to be widely used in the treatment of anaphylaxis. Most of the second-generation H1 antihistamines have low aqueous solubility and none is available in formulation for injection.[2]

Antihistamines also have a potential role in prevention of anaphylaxis. In idiopathic urticaria, patients with frequent episodes, that is, more than 6 in 1 year or more than 2 in 2 months, are reported to benefit from prophylactic treatment with an H1-antihistamine.[85] Second-generation H1 antihistamines, administered orally, prevent allergic reactions in patients receiving immunotherapy.[86]

Table 1. Formulations and dosages of second-generation oral antihistamines

Generic name	Formulation		Pediatric recommended dose
	Tablet	Syrup	
Cetirizine	10 mg	5mg/5ml	2.5 -5 mg od (6mo- 5 yr) 5-10 mg od (6-11 yr)
Loratidine	10 mg	5mg/5ml	5 mg od (2-9 yr) or 10 mg od (6-11 yr)
Desloratidine	5 mg	NA	5 mg od (≥ 12 yr)
Fexofenadine	60, 120, 180 mg	NA	60 mg bd or 120-180 mg od (≥ 12 yr)
Levocetirizine	5mg	NA	5 mg od (≥ 6 yr)

Od: once daily, NA: Not available, mo: month, yr: year

Adapted from Motala 2009.[2]

Conclusion

H1-antihistamines have a major role in allergic diseases; they are the main stay medications in allergic rhinoconjunctivitis and urticaria. Second-generation H1 antihistamines are preferred and more widely used owing to their better safety profile and efficacy than first-generation H1 antihistamines. First- generation

H1 antihistamines are reserved for clinical situations where sedation or parenteral route is needed. More studies are needed to evaluate H1 antihistamines efficacy, therapeutic regimens and adverse effects in pediatric allergic disorders.

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