

When Safety matches Efficacy: "Second generation Antihistamine"

Ariyanto Harsono MD, PhD

Department of Pediatric Allergy-Immunology Division, Medical Faculty, Airlangga University, Surabaya, Indonesia.

Abstract.

Histamine is an important chemical mediator of inflammation, vasodilation, increased vascular permeability, decreased peripheral resistance, airway smooth muscle contraction, and sensory nerve stimulation causing itching. It also plays a significant role in neurotransmission and in cardiac function.

In allergic rhinoconjunctivitis and urticaria, there is strong evidence for the role of H₁-antihistamine treatment. In asthma, additional dose–response studies, including higher doses of antihistamines than those used in allergic rhinitis, are needed to determine the role of antihistamines. In atopic dermatitis, the itch-relieving topical glucocorticoid-sparing effects of H₁-antihistamines also require further documentation.

The potential benefits of each H₁-antihistamine should be weighed against the potential risks, and second-generation H₁-antihistamines with excellent, well-documented safety records should be used in preference to older, less safe H₁-antihistamines. Second-generation H₁-antihistamines are more relevant than ever in the treatment of allergic disorders.

Abstrak.

Histamin telah dikenal sebagai mediator antiinflamasi, vasodilatasi, peningkatan permeabilitas pembuluh darah, penurunan resistensi perifer, kontraksi otot polos jalan nafas, dan merangsang saraf sensoris yang memberikan rasa gatal. Di samping itu juga mempunyai peranan penting pada transmisi system syaraf dan fungsi jantung.

Penggunaan antihistamin H₁ untuk pengobatan rino-konjungtivitis dan urtikaria telah terbukti efektif. Penelitian respon dosis antihistamin, serta penggunaan dosis antihistamin yang lebih besar (dibanding untuk rinitis alergika) diperlukan untuk menentukan peranan antihistamin pada penatalaksanaan asma. Diperlukan glukokortikoid topikal sebagai "sparing" untuk mengurangi keluhan gatal pada dermatitis atopi.

Keuntungan dan kerugian harus selalu menjadi dasar pertimbangan pemilihan antihistamin H₁. Dengan mempertimbangkan keunggulan dan keamanan dibandingkan generasi terdahulu, antihistamin H₁ generasi ke-2 lebih tepat dipilih untuk terapi penyakit-penyakit alergi.

*Keywords:*H₁-antihistamine, allergic rhinitis, urticaria, asthma, atopic dermatitis, efficacy, safety.

INTRODUCTION.

Histamine, an important chemical mediator of allergic inflammation, is produced and stored in cytoplasmic granules in tissue mast cells and basophils, from which it is released in large quantities by noncytotoxic mechanisms during the early allergic response.^{1,2}

Acting at H₁- and H₂-receptors, histamine induces the vascular endothelium to release nitric oxide, which stimulates guanyl cyclase and increases cyclic guanosine monophosphate in the vascular endothelial cells, causing vasodilation, erythema, increased

vascular permeability, and edema. The vasodilation is enhanced by an axon reflex resulting from the release of substance P by antidromic conduction on afferent C fibers. The affinity of histamine for H₁-receptors in the vasculature is approximately 10 times its affinity for H₂-receptors. Acting at H₁- and H₂-receptors, histamine also reduces peripheral resistance, lowers blood pressure, and has positive inotropic effects.

Histamine also causes contraction of smooth muscle in the airway, chronotropic effects in the heart, and stimulation of sensory nerve endings, causing itching of the mucosa and skin through stimulation of thin, nonmyelinated afferent C fibers, which have low conduction velocity and large enervation territories.³

H₁-receptors have G-protein-coupled receptor characteristics,⁴ and the gene encoding them has been cloned and expressed in human cells. It has recently been shown that these receptors demonstrate agonist-independent signal transduction. H₁-antihistamines inhibit this constitutive signaling, probably by stabilizing an inactive conformation of the H₁-histamine receptor and acting as inverse agonists.⁴

Cloning, functional expression, and constitutive activity have also been shown for H₂-receptors, which are G-protein-coupled receptors located in the stomach, cardiovascular system, and skin vasculature.

Recently, H₃-receptors, which are autoreceptors regulating the release and biosynthesis of histamine, and H₄-receptors, which are found on leukocytes throughout the body, have been discovered. Molecular aspects of H₁-, H₂-, H₃-, and H₄-receptors are being extensively investigated with regard to receptor biochemistry, molecular biology, and signal transduction.⁴

H₁-antihistamines: clinical pharmacology

Traditionally, the efficacy of H₁-antihistamines in allergic disorders is attributed primarily to downregulation of activity at H₁-receptors on the endothelial cells of the postcapillary venules, resulting in decreased vascular permeability, decreased exudation of fluid, protein, and cells, and increased peripheral resistance. H₁-antihistamines also downregulate the effect of histamine at H₁-receptors on airway smooth muscle, resulting in bronchodilation, and on afferent C fibers, resulting in decreased mucosal and cutaneous itching. In addition, H₁-antihistamines have antiallergic and additional anti-inflammatory effects.^{5,6} Some of these, for example, suppression of mediator release from mast cells and basophils, occur independently of the H₁-receptor and are probably not clinically relevant. Other effects, such as the downregulation of nuclear factor kappa beta and generation of cytokines and adhesion molecules, are H₁-receptor dependent and are more likely to result in clinical benefits.

H₁-antihistamine potency and specificity have been assessed in vitro by using various cell systems and in vivo in animal models. Clinical efficacy in humans depends not only on H₁-antihistamine potency and specificity but also on the H₁-antihistamine concentration at receptor sites and therefore on its pharmacokinetic properties: the absorption, distribution, metabolism, and elimination of the H₁-antihistamine in the body.⁷⁻¹⁴

The pharmacodynamics of H₁-antihistamines can be investigated in the mucosa of the upper and lower airways^{7,13} and in the skin,⁷⁻¹⁰ which is the most commonly studied site because of its accessibility.

After oral administration in usual doses, many second-generation H₁-antihistamines achieve peak concentrations rapidly in the skin.⁷⁻¹⁰ Suppression of the histamine-induced wheal and flare or of the allergen-induced early allergic response and the late allergic response is a useful bioassay for defining dose-response curves and for identifying clinically relevant differences in onset of H₁-antihistamine activity, maximum activity, and duration of activity. Most H₁-antihistamines have an onset of action within 1 to 2 hours after

administration and have a 24-hour duration of action after a single dose. “Maps” of the pharmacokinetic/pharmacodynamic relationship of H₁-antihistamines define the plasma concentration/activity relationship for each of these medications.⁸ During long-term regular daily administration of H₁-antihistamines, their activity does not wane, as evidenced by undiminished ability to suppress the wheal and flare and to decrease symptoms in persistent allergic rhinitis and chronic urticaria during weeks and months of treatment.^{1,2,7}

Efficacy of H₁-antihistamines in the treatment of allergic disorders

Allergic rhinitis

Allergic rhinitis is the most prevalent chronic disorder in the world, currently affecting more than 40% of young people in some countries.¹⁵ The recent Allergic Rhinitis and its Impact on Asthma guidelines proposed that seasonal allergic rhinitis, or rhinitis in which symptoms occur on fewer than 4 days per week or fewer than 4 weeks per year, be renamed intermittent rhinitis, and that perennial allergic rhinitis in which symptoms occur on more than 4 days per week and for more than 4 weeks per year be renamed persistent rhinitis.¹⁵ H₁-antihistamines, either administered orally or applied topically to mucosal surfaces, are the most commonly used first-line medications for both intermittent (seasonal) and persistent (perennial) allergic rhinitis. There are many more studies of intermittent (seasonal) rhinitis than there are of persistent (perennial) rhinitis.¹⁵

Level 1A evidence supporting the use of the second-generation, nonsedating H₁-antihistamines such as cetirizine, fexofenadine, and loratadine in intermittent and persistent allergic rhinitis has been obtained in thousands of patients in prospective, randomized, double-blinded, placebo-controlled clinical trials of 1 to 4 weeks' duration and in short-duration studies conducted outdoors at the height of the pollen season in intermittent rhinitis.^{1,2,15-20} In recent, randomized, double-blinded, placebo-controlled studies, desloratadine, levocetirizine, and tecastemizole have also been found to be effective in allergic rhinitis.^{11,12}

Generally, the patients enrolled in allergic rhinitis studies have moderate symptoms and positive epicutaneous test results to at least 1 relevant airborne allergen. The outcomes are assessment of total reflective and instantaneous symptom scores, as well as scores for individual symptoms performed at the end of the dose interval.

In allergic rhinitis, compared with placebo, H₁-antihistamines consistently and significantly reduce sneezing; rhinorrhea; itchy, watery, red eyes; and itchy nose, palate, or throat, and in some studies even reduce nasal congestion. The dose-response curve for relief of symptoms with H₁-antihistamines is relatively flat. In comparative studies it is uncommon to find statistically significant and clinically relevant differences among the H₁-antihistamines).^{16,17} H₁-antihistamines are less effective than intranasal glucocorticoids in moderate/severe persistent rhinitis characterized by troublesome symptoms, sleep disturbance, and impairment of daily activities including school, work, and leisure.¹⁸ In one study H₁-antihistamines have been found to have similar efficacy to leukotriene modifiers in relieving sneezing, rhinorrhea, itching, and even congestion.¹⁹ H₁-antihistamines are more effective than decongestants for relief of sneezing, rhinorrhea, and itching but less effective than decongestants for relief of nasal congestion.²⁰

Asthma

Traditionally, H₁-antihistamines have been generally considered to be ineffective in asthma unless given at high doses.^{21,22} Recently, however, in doses recommended for the treatment of intermittent allergic rhinitis, cetirizine, desloratadine, and loratadine have been reported to improve coexisting mild “seasonal” asthma symptoms, to reduce β_2 -agonist requirements, and even to improve pulmonary function significantly.^{21,23} This is not surprising in view of the fact that asthma and allergic rhinitis have similar epidemiologic, histologic, physiologic, and immunopathologic characteristics and that the key to managing both

disorders is prevention and relief of chronic allergic inflammation in both the upper and lower airways.²⁴ Additional dose-ranging studies of H₁-antihistamines are needed in patients with allergy and mild asthma.

Acute and chronic urticaria

In acute and chronic urticaria, H₁-antihistamines are the cornerstone of symptomatic treatment^{25,26,27} There is Level 1A evidence for their beneficial effects, particularly for the relief of itching, but also for reducing the number, size, and duration of urticarial lesions.^{27,28} The dose-response curve for efficacy is relatively flat.²⁷ Relief of wheal and flare (erythema) might be incomplete, because the vascular effects of histamine are mediated through its action at H₂-receptors as well as at H₁-receptors and are also mediated by other vasoactive substances, including proteases, eicosanoids such as leukotrienes and prostaglandin E₁, and neuropeptides such as substance P.

For optimal effectiveness in chronic urticaria, H₁-antihistamines should be given on a regular basis rather than as needed.

In randomized, prospective, double-blinded, placebo-controlled studies, the second-generation, relatively nonsedating H₁-antihistamines have been found to be as effective as the first-generation, more sedating agents.²⁸ H₁-antihistamines have not been optimally studied in some types of chronic urticaria (eg, in the physical urticarias). The response to H₁-antihistamine treatment in other types of urticaria (eg, in urticarial vasculitis) is unsatisfactory.

An H₂-antihistamine administered concurrently with an H₁-antihistamine might modestly enhance relief of itching and wheal formation in some patients with urticaria refractory to treatment with an H₁-antihistamine alone.²⁹ The available evidence does not justify the routine addition of H₂-antihistamine treatment to H₁-antihistamine treatment.²⁵

Atopic dermatitis

H₁-antihistamines are administered orally in conjunction with topical glucocorticoids to relieve itching in atopic dermatitis. The evidence base for their use in this disorder is considerably weaker than it is in urticaria,³⁰ and higher doses than those used in urticaria might be needed.³¹

Infants and young children with atopic dermatitis and/or elevated serum IgE level and a family history of atopy are at increased risk for the development of asthma and other allergic disorders. A randomized, prospective, placebo-controlled, double-blinded study of 18 months' duration, with a 6-month double-blinded follow-up, was conducted in 817 children, who were enrolled between their first and second birthdays. FDA had approved cetirizine in infant as young as 6 months. Regular treatment with high-dose (0.25 mg/kg twice a day) cetirizine had a significant topical glucocorticoid-sparing effect in atopic dermatitis treatment.³² It also significantly reduced the number of acute urticaria episodes,²⁶ delayed the development of asthma in subsets of children who were sensitized to grass pollen and house dust mite at study entry³³ (although not in the intention-to-treat population, the primary outcome of the study), and did not cause any significant adverse effects.³⁴

Safety of H₁-antihistamines

H₁-antihistamines as a class have the potential to produce a wide variety of short-term and long-term adverse effects (Table 1).³⁵ The nonsedating H₁-antihistamines are relatively specific for the H₁-receptor, and because they have little affinity for muscarinic cholinergic, α -adrenergic, or serotonergic receptors, they do not cause dry mouth, urinary dysfunction, constipation, diplopia, hypotension, tachycardia, or weight gain.

Table 1. Potential adverse effects of H₁-antihistamines

	Comments
Potential short-term effects	
CNS toxicity: sedation and psychomotor impairment	Adverse effects are common after all first-generation oral H ₁ -antihistamines and are because of H ₁ activity; they are uncommon after second-generation H ₁ -antihistamines
Cardiac toxicity	Adverse effects are uncommon and produced mostly by terfenadine or astemizole; they are caused by blockade of ion channels and do not involve the H ₁ receptor
Other adverse effects	
Peripheral anticholinergic effects, eg, dry mouth, urinary retention	Common after first-generation H ₁ -antihistamines; uncommon after second-generation antihistamines
Weight gain	Reported after cyproheptadine, astemizole, or ketotifen
Dysgeusia (bitter taste)	Reported after azelastine ingestion; less common after azelastine intranasally
Potential long-term effects	
Carcinogenicity	Not a problem with currently available H ₁ -antihistamines, because regulatory agencies do not approve carcinogenic medications; if, after approval, suspicion of carcinogenicity arises, prompt withdrawal occurs
Tumor promotion	No evidence in humans
Teratogenicity	Not a problem with currently available H ₁ -receptor antagonists, because regulatory agencies do not approve teratogenic medications; occasional associations have been reported, because up to 5% of infants have a congenital anomaly and H ₁ -antihistamines are ubiquitously used; causality has not been confirmed in prospective, observational, first-trimester studies

Data from reference 35.

[†]Terfenadine and astemizole are no longer approved for use by regulatory agencies.

Central nervous system toxicity

Histamine is an important neurotransmitter in the central nervous system (CNS). Histaminergic neurons are located in the tuberomammillary body in the posterior hypothalamus, and varicose fibers containing histamine project to almost all regions of the brain, including the cerebral cortices. In H₁-receptor knockout mice, the modulatory role of brain histamine on cortical arousal mechanisms has been clearly demonstrated, and the absence of H₁-receptors is associated with aggression, locomotion problems, memory deficits, and other neurologic symptoms.³⁶

In humans, sedating H₁-antihistamines such as chlorpheniramine and diphenhydramine cross the blood–brain barrier and occupy more than 80% of H₁-receptors, even at low doses with minimal peripheral H₁ activity (eg, chlorpheniramine 2 mg). In ordinary doses, they therefore block the neurotransmitter effects of histamine and produce somnolence and impair vigilance, psychomotor performance, cognitive function, and learning.^{37–39} These adverse CNS effects are similar in magnitude to those produced by alcohol or tranquilizers. Patients are often unaware of the psychomotor impairment produced by the first-generation H₁-antihistamines, because they might not perceive sedation or drowsiness. Tolerance to the adverse CNS effects does not necessarily develop, and bedtime dosing does not decrease daytime CNS impairment. Also, the adverse CNS effects might not be counteracted by concomitant administration of a CNS stimulant such as the decongestant pseudoephedrine.^{2,35}

In contrast, the second-generation H₁-antihistamines such as cetirizine, fexofenadine, and loratadine have less potential to cross the blood–brain barrier because of their physicochemical properties (strong plasma protein–binding/hydrogen-binding capacity and either very high or very low lipophilicity). They have been shown to occupy fewer than 20% of

H₁-receptors even at high doses⁴⁰ and to block neurotransmission by histamine in the CNS to a lesser degree than the sedating antihistamines.

Many prospective, randomized, crossover, double-blinded, placebo-controlled studies of the potential adverse effects of H₁-antihistamines on the CNS have been performed.⁴¹⁻⁴⁴ In these studies, objective measurements of sleep and of learning, memory, and psychomotor function have been made at regular intervals. The nonsedating H₁-antihistamines differ more in their CNS effects than in their peripheral antihistaminic effects. Even at doses in excess of those recommended by the manufacturer, fexofenadine has an effect on the CNS comparable to placebo⁴³⁻⁴⁵; however, some relatively nonsedating H₁-antihistamines such as cetirizine and loratadine have dose-related CNS adverse effects. Objective studies of the CNS effects of the newest H₁-antihistamines desloratadine, levocetirizine, and tecastemizole have recently been performed.

Cardiac toxicity

The cardiac action potential results from a dynamic balance between inward depolarizing sodium and calcium currents and outward potassium repolarizing currents. During a cardiac cycle, the resulting repolarization phase from all ventricular cells is represented by the QT interval on the surface electrocardiogram.⁴⁶⁻⁴⁸ The earliest nonsedating H₁-antihistamines astemizole and terfenadine are associated with blockade of delayed rectifier potassium current channels and prolongation of the monophasic action potential (QT interval), which might then induce the development of early after-depolarization and dispersion of repolarization leading to torsades de pointes through reentry mechanisms.^{46,47} These medications are no longer approved by regulatory authorities in most countries.

Unlike terfenadine and astemizole, the nonsedating H₁-antihistamines cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine, and tecastemizole lack cardiotoxic potential.

In preclinical studies the potassium channels encoded by the human ether-a-go-go-related gene that represent the molecular basis of the IKr channel have facilitated in vitro comparative studies of the cardiotoxic potential of these medications.^{48,49}

In humans, cetirizine, fexofenadine, and loratadine have been extensively investigated for potential cardiac toxicity, and no adverse effects on the cardiovascular system have been detected at therapeutically relevant doses, even when these doses are vastly exceeded. Their lack of cardiac toxicity has been confirmed by using drug prescription event monitoring in tens of thousands of patients in post marketing surveillance studies.⁵⁰ In clinical trials to date, desloratadine, levocetirizine, and tecastemizole also appear to be free from cardiac toxicity.

Summary

The evidence base for the use of H₁-antihistamines in the treatment of allergic disorders continues to evolve and is particularly strong in allergic rhinoconjunctivitis and urticaria. The relative efficacy and safety of interesting new medications in this class are currently being evaluated. H₁-antihistamines are more relevant than ever in the treatment of allergic disorders. Second generation H-1 antihistamine is safe and effective, and among these drugs, cetirizine has been recommended in long term use in infants as young as 6 months.

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