

Appraisal of the validity of histamine-induced wheal and flare to predict the clinical efficacy of antihistamines

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Antihistaminic drugs have been used successfully for many years in the treatment of allergic diseases. Second-generation antihistamines have fewer sedating side effects than first-generation agents, and the number of newer drugs available for clinical use is growing. Various methods have been used to assess antihistaminic activity, the most popular of which is the epicutaneous histamine-induced wheal and flare. This test relies on the ability of epicutaneously injected histamine to bring about the wheal and flare, a neurovascular response that involves reflex vasodilation (flare) and local swelling caused by plasma extravasation (wheal). Antihistamines have been compared on the basis of their ability to block the histamine-induced wheal and flare in the skin. Results of these trials have been applied to predict the global antiallergic efficacy of various antihistamines. This review has examined the reliability of suppression of the histamine wheal and flare reaction in the skin to predict an antihistamine's clinical efficacy in two common allergic diseases, seasonal allergic rhinitis and chronic idiopathic urticaria. Although histamine is one mediator in the allergic response in the skin and nasal mucosa, many other agents are important modulators of the allergic response. In addition, the major structural and functional differences that exist between the nasal mucosa and the skin affect the type of local response. These manifest themselves as differences between the responses to antigen and histamine challenge in the skin and the nose. The allergic responses in these tissues are not simply the consequence of one chemical but are the result of a cascade of interactions among various cells and mediators. The clinical manifestations of these complex interactions obviously cannot be fully replicated by injection of one chemical mediator, histamine, into the outer layer of the skin.

Studies with antihistamines have shown that certain drugs, such as cetirizine, are more suppressive than others (loratadine, terfenadine) in controlling the histamine-induced wheal and flare reaction in the skin. When the clinical efficacy of these medications is compared in clinical trials in seasonal allergic rhinitis and chronic idiopathic urticaria, all are equally efficacious in controlling symptoms. Although the histamine-induced wheal and flare reaction can serve as a useful clinical pharmacologic test to assess dose-response relations for an antihistamine, its lack of correlation with clinical responses among antihistamines indicates that this model should not be used to predict or compare clinical efficacies of antihistamines in seasonal allergic rhinitis and chronic idiopathic urticaria. (J Allergy Clin Immunol 1997;99:S798-806.)

Key words: Histamine-induced wheal and flare, antihistamines, seasonal allergic rhinitis, chronic idiopathic urticaria, antiallergic efficacy

Historically, the study of histamine-receptor antagonists reaches back nearly 60 years to the discovery of the first H₁-receptor antagonist by Bovet and Staub in 1937.¹ The first-generation antihistamines saw wide clinical use in allergic diseases from the 1940s onward, but major central nervous system (CNS) adverse events, such as sedation and performance deficits, curtailed their subsequent use. They also interacted with other systems, such as the cholinergic system, because of coexisting anticholinergic activity. The impetus for the development of

Abbreviations used

CGRP:	Calcitonin gene-related peptide
CIU:	Chronic idiopathic urticaria
CNS:	Central nervous system
EDRF:	Endothelium-derived relaxing factor
EPR:	Early-phase response
LPR:	Late-phase response
LT:	Leukotriene
NKA:	Neurokinin A
PG:	Prostaglandin
SAR:	Seasonal allergic rhinitis
VIP:	Vasoactive intestinal peptide

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nonsedating antihistamines with retained, or enhanced, antiallergic activity led to the second-generation agents used today. Second-generation antihistamines, such as

loratadine, astemizole, and terfenadine, have essentially supplanted the older drugs because they exhibit an improved CNS adverse-event profile and are free of significant sedation and anticholinergic actions. Cetirizine, also a second-generation antihistamine, is less sedating than antihistamines of the first generation; however, in clinical trials, dose-related somnolence has been observed.

With the list of second-generation antihistamines growing significantly, much interest has focused on comparing the relative efficacies of the various compounds. For this purpose, laboratory and clinical approaches have been used with varying results. The most common comparative tool used in human antihistamine pharmacodynamic research involves the epicutaneous injection of histamine. The response that follows an epicutaneous histamine injection, known as the wheal and flare, comprises areas of swelling (wheal) and vasodilation (flare) at the injection site. An easily performed procedure, this test is based on the ability of systemically circulating antihistamine to block the histamine-induced wheal and flare response.

Because there appears to be an obvious pharmacologic link of histamine to antihistamine, researchers have viewed the suppression of the histamine-induced wheal and flare in the skin as a useful clinical pharmacologic test to assess dose-response relations of or among antihistamines and to correlate the test results with plasma levels of the drugs. Bioassay of H_1 -receptor blockade, however, is reasonable only if the antihistamine has no effect other than that and if the blockade effect is only on blood vessels.

Although histamine is an important mediator in allergic responses, the cascade of events involving cells, nerves, blood vessels, and various mediators is complex; histamine is only one of the many important agents involved. Empirically, it appears inappropriate to assume that a correlation exists between the simple pharmacologic interaction of histamine with an antihistamine localized in the skin and the relief of tissue- and organ-allergic inflammatory responses and of clinical symptoms in allergic diseases, which themselves are the final manifestations of complex interactions of chemical mediators and specialized cells. This oversimplification is evident when comparing the different mechanisms underlying the physiologic responses to allergens in the skin and in the nasal mucosa and the skin wheal and flare reaction elicited by the epicutaneous injection of histamine. Most relevant, when the clinical efficacy of these medications is compared in clinical trials in seasonal allergic rhinitis (SAR) and chronic idiopathic urticaria (CIU), all are equally efficacious in controlling symptoms. How reliable, therefore, is this skin test in predicting and comparing the clinical efficacy of antihistamines in two common allergic diseases, SAR and CIU?

The purpose of this review is to evaluate any correlation between comparative inhibition of the histamine-induced skin wheal and flare reaction and the clinical

efficacy of antihistamines in the treatment of SAR and CIU. We examine the findings in published comparative clinical pharmacodynamic studies of antihistaminic agents that report the suppression of the histamine-induced wheal and flare, and we compare them with the outcomes of clinical efficacy trials of these same drugs in those allergic diseases.

THE HISTAMINE-INDUCED CUTANEOUS WHEAL AND FLARE REACTION

The allergic response in the skin to allergens can be divided into early and late phases that differ on the basis of initiation, duration, and components involved in the reaction. The phased responses are the consequence of sequential interactions of allergen and antibody and the release of a host of chemical mediators. The early-phase response (EPR) is triggered by the binding of antigen to IgE, which results in a cascade of mediator releases. These mediators are the initiators of the late-phase response (LPR). Although the EPR occurs over a period of minutes to an hour, the LPR begins more than 1 hour after an allergen-IgE interaction and can last for 6 to 48 hours. The major cellular component of the EPR is the mast cell, whereas the LPR involves cytokine production leading to granulocyte recruitment, particularly basophils and eosinophils.

On the other hand, the histamine-induced wheal and flare response occurs rapidly and does not persist for longer than 1 hour or so, suggesting that this reaction is the result of activation of parts of the EPR pathway without manifestation of the LPR. The full EPR, therefore, does not follow epicutaneous histamine injection, because mast cell degranulation and multiple mediator release do not occur. Although the histamine-induced wheal and flare response outwardly resembles the cutaneous EPR, histamine injection does not accurately mimic the natural response to allergen in the skin, nor does it allow evaluation of other potentially important antiallergic effects of the newer antihistamines. These effects include inhibition of mediator release from mast cells and inhibition of the LPR.

In trying to understand the mechanisms underlying the cutaneous histamine-induced wheal and flare response and the role of antihistamines in its suppression, it is important to note that other mediators involved in the full response to allergens in the skin are bypassed after histamine injection. For example, after administration of the antihistamine astemizole for 8 weeks, the histamine-induced wheal and flare reaction was strongly suppressed.² With the same pretreatment, however, astemizole was less effective in inhibiting allergen-induced wheal and flare reactions. One interpretation of this finding is that the response after the epicutaneous injection of the usual pharmacologic doses of histamine used in these tests is not fully analogous to the activation of cutaneous IgE-loaded mast cells by an allergen. Antihistamines can suppress the histamine-induced wheal and flare by blocking the binding of histamine to its receptors on nerves, vascular smooth muscle, endo-

TABLE I. Physiologic responses to histamine challenge and the mechanisms underlying these responses in the skin and the nasal mucosa

	Response	Mechanism
Skin		
Wheal	Increased vascular permeability	H ₁ -receptor-mediated endothelial cell contraction (via EDRF (NO)/PGI ₂)
Flare	Vasodilation	H ₁ /H ₂ -receptor mediated axonal reflex (Substance P/CGRP/NKA-mediated)
Nasal Mucosa		
Itch	Sensory nerve activation	H ₁ -receptor-mediated trigeminal nerve activation
Congestion	Increased mucosal blood flow (vasodilation)	H ₁ /H ₂ -receptor-mediated stimulation of sympathetic nerves. VIP release from parasympathetic (?) nerves.
Rhinorrhea	Increased secretion from goblet cells and increased vascular permeability	H ₁ -receptor interaction with parasympathetic nerves (goblet cells). H ₁ -receptor mediated increase in engorgement (sympathetic) of highly fenestrated capacitance vessels.

NO, Nitric oxide; PGI₂, prostaglandin I₂.

thelium, and mast cells, but they cannot fully suppress the cutaneous responses to the epicutaneous injection of other important mediators, such as eicosanoids, substance P, and calcitonin gene-related peptide (CGRP).

In summary, the wheal and flare response after the epicutaneous histamine injection mimics the early phase of the allergic response, but mast cell degranulation and the subsequent release of mediators from mast cells, neurons, and other cells along with the influx of granulocytes (LPR) do not occur.³ The histamine-induced wheal and flare, therefore, does not involve the cellular and mediator mechanisms responsible for the production of the full allergic response, as seen with allergen skin challenge.

ALLERGEN SKIN TESTING

The mechanisms outlined above relate only to the histamine-induced wheal and flare in the skin. The responses to allergens in the skin and in the nasal mucosa differ significantly from the cutaneous response to histamine injection.

When an allergen is introduced into the skin, as in skin prick or scratch tests, the interaction between the antigen and IgE on the surface of mast cells in the skin results in cross-bridging, leading to a cascade of intracellular reactions. The intracellular G-protein pathway results in the activation of phospholipase C³ and of other processes in the mast cell that lead to a large increase in intracellular calcium levels.⁴ Degranulation follows with the release of histamine from the extruded granules and the production of associated secretagogues. The released histamine and other agents (leukotriene (LT) B₄, LTC₄, prostaglandin (PG) D₂, heparin, and neutral proteases) cause local vasodilation (the flare) and increased vascular permeability, the final result of which is plasma extravasation and formation of a swollen area (the wheal). This entire process, which constitutes the EPR, occurs over a period of few minutes to 1 hour. The

swelling of the cutaneous allergic reaction, which evolves gradually into the LPR over the next 3 to 5 hours, is characterized by an influx of inflammatory cells. As described above, epicutaneous histamine injection does not produce the above-described cascade in the EPR and, relevantly, is not associated with the LPR, thereby mimicking only part of the natural cutaneous response to allergen.

ALLERGEN CHALLENGE IN THE NOSE

In the nasal mucosa, allergens similarly bind to IgE-loaded mast cells, causing degranulation and the release of mediators, such as histamine, toluenesulfonylarginine methyl ester (TAME)-esterase, leukotrienes, and PGD₂. The EPR after allergen exposure or challenge occurs directly after mast cell degranulation and leads to three clinically evident responses. The first, sneezing, results from histamine-associated sensory neural activation. The second is hypersecretion from glandular tissue (and goblet cells), which is under parasympathetic nervous system control and local mediators. Third, nasal mucosal congestion results from sympathetically and parasympathetically controlled vascular engorgement and is associated with increased blood flow with vasodilation and increased capillary permeability within the nasal vasculature.

Rhinorrhea occurring during the EPR results from increased glandular activity controlled by parasympathetic nerves and the passage of plasma and large-molecular-weight proteins through the fenestrated capillaries of the nasal vasculature. Histamine released locally from mast cells modulates rhinorrhea, possibly via interactions with the sympathetic/parasympathetic systems or by acting directly with mucosal glands, goblet cells, or blood vessels. Nasal mucosa glandular secretion is controlled parasympathetically.⁵ If antigen-induced mast cell activation in the nose were mediated by nerves alone, changes in histamine and PGD₂ levels would

TABLE II. Review of pharmacodynamic studies of antihistamine suppression of the cutaneous histamine-induced wheal and flare reaction

Reference	Trial	Patients (n)	Drug	Duration	Suppressive effects*
Roman et al. ⁹	DB, PC	60	L 10 mg OD L 20 mg OD L 40 mg OD Chl 12 mg OD	4 weeks	Wheal only L 40 mg > L 20 mg > L 10 mg > P = Chl
Small ¹⁰	DB, PC, X	51	C 10 mg OD L 10 mg OD	1 week	C = L > P
Van Rooy and Janssens ¹¹	DB, Para	30	C 10 mg OD L 10 mg OD T 120 mg OD A 10 mg OD E 10 mg OD	1 week	Wheal: E > A > L > C > T Flare: A > E > C > L > T
Paul et al. ¹²	DB, PC	24	C 10 mg OD L 10 mg OD T 60 mg BID Cl 2 mg OD	3 days	C > T > L > Cl > P
Shall et al. ¹³	SB, PC, X	24	C 10 mg OD L 10 mg OD T 60 mg OD T 120 mg OD	1 day	C > T 120 mg > T 60 mg > L > P
Simons et al. ¹⁴	DB, PC, X	20	C 10 mg OD L 10 mg OD T 60 mg OD T 120 mg OD Ast 10 mg OD Chl 4 mg OD	1 day	C > T 120 mg > T 60 mg > L > A > Chl
Rosenzweig et al. ¹⁵	DB, PC, X	15	C 10 mg OD L 10 mg OD T 120 mg OD M 10 mg OD	1 day	Wheal: M > T > C > L Flare: C > T > M > L
Lever et al. ¹⁶	DB, PC, X	12	T 120 mg OD C 10 mg OD L 10 mg OD	1 day	T = C > L > P
Humphreys and Hunter ¹⁷	X	10	C 10 mg OD Ast 10 mg OD L 10 mg OD	1 week	C > A > L
Kontou-Fili et al. ¹⁸	DB, X	10	C 10 mg OD L 10 mg OD	1 day	C > L > P
Pechadre et al. ¹⁹	DB, PC, X	9	C 10 mg OD T 60 mg OD	1 day	C > T > P
Rihoux and Dupont ²⁰	DB, PC, X	9	C 10 mg OD T 180 mg OD	1 day	C > T > P
Fadel et al. ²¹	DB, PC, X	7	L 10 mg OD C 10 mg OD	1 day	C > P > L

DB, Double-blind; P, placebo; PC, placebo-controlled; X, crossover; C, cetirizine; L, loratadine; Ast, astemizole; T, terfenadine; E, ebastine; M, mizolastine; Cl, clemastine; Chl, chlorpheniramine; OD, once daily; BID, twice daily; TID, three times daily.

*The > sign refers to the first antihistamine being more effective in the suppression of the wheal and flare reaction due to histamine injection in the skin with respect to the second antihistamine (i.e., the differences are significant). The = sign refers to the two antihistamines not being significantly different in the suppression of the wheal and flare reaction after histamine injection in the skin.

occur in parallel with sneezing. Baroody et al.,⁶ however, demonstrated that pretreatment with cetirizine had no effect on histamine and PGD₂ release (PGD₂ is a marker of mast cell activation) even though sneezing was reduced, confirming the observation that antigen-induced activation of mast cells occurs via antigen-antibody interactions and is not a result of neural reflexes.

The response to allergen does not end with mast cell

degranulation. A late-phase inflammatory response follows. During the LPR, one of the many events is that basophils enter the nasal mucosa within hours after antigen stimulation and are the source of histamine. The role of this autacoid in the LPR, however, is unknown.

Although increases in PGD₂ and tryptase are associated with release of histamine (from mast cells) during the immediate response, these products are not present

TABLE III. Comparative placebo-controlled studies of antihistamines and their efficacy in the treatment of CIU

Reference	Study type	Patients (n)	Drug	Duration (wk)	Symptom control*
Breneman et al. ²²	DB, PC	187	C 10 mg OD Ast 10 mg OD	4	C > A > P
Belaich et al. ²³	DB, PC	172	L 10 mg OD T 60 mg BID	4	L > P T > P
Grant et al. ²⁴	DB, PC	122	T 60 mg BID Chl 4 mg TID	6	T > Chl > P
Guerra et al. ²⁵	DB, PC	116	L 10 mg OD C 10 mg OD	4	L > C > P
Alomar et al. ²⁶	DB, PC	47	C 10 mg OD Ast 10 mg OD	4	C > A > P
Dockx et al. ²⁷	DB, PC, X	29	C 10 mg OD T 60 mg BID	2	C > P T > P
Go et al. ²⁸	DB, X	28	C 10 mg OD T 60 mg BID	2	C = T > P
Kint et al. ²⁹	DB, PC, X	27	C 10 mg OD T 60 mg BID	6	C > P T > P

Abbreviations as in Table II.

*The > sign refers to the first antihistamine being more effective in the suppression of the commonly measured symptoms of urticaria (itch, erythema) with respect to the second antihistamine. The = sign refers to the two antihistamines not differing with respect to the above parameters.

TABLE IV. Direct comparative studies (no placebo) of antihistamines and their efficacy in the treatment of CIU

Reference	Study type	Patients (n)	Drug	Duration (wk)	Symptom control*
Guillet et al. ³⁰	DB	166	L 10 mg OD C 10 mg OD	1	L = C
Marcher and Eichelberg ³¹	DB	84	C 10 mg OD T 60 mg BID	6	C > T
D'Ambrosio et al. ³²	DB, Para	42	C 10 mg OD T 120 mg OD	3	C = T
Mauracher and Riches ³³	DB	40	L 10 mg OD Ast 10 mg OD	4	L = Ast

Para, parallel. Other abbreviations as in Table II.

*The > sign refers to the first antihistamine being more effective in the suppression of the commonly measured symptoms of urticaria (itch, erythema) with respect to the second antihistamine. The = sign refers to the two antihistamines not differing with respect to the above parameters.

during the late response. If basophils play the major role during the LPR, what are the implications regarding the specificity of the stimulus that causes histamine release during this time and for the pharmacologic control of late-phase mediator release given that pharmacologic regulation of mast cells and basophils differ? All of this is far removed from the simpler local effects occurring in the skin after epicutaneous injection of histamine.

HISTAMINE CHALLENGE IN THE NOSE

Nasal topical histamine challenge entails the spraying of histamine solution onto the nasal mucosa, eliciting itching, sneezing, rhinorrhea, and nasal congestion that closely resemble the early response to allergen. These clinical consequences and the explanations for their origins are significantly different from those of the cutaneous wheal and flare reaction. These differences are outlined in Table I. As in the skin, however, histamine challenge in the nose does not lead to cellular

infiltration and an LPR. Topical histamine provocation results in the generation of kinins but does not induce a late inflammatory response or the generation of LTC₄ and does lead to sneezing, itching, rhinorrhea, and congestion within minutes, all symptoms of an acute bout of allergic rhinitis.

In conclusion, histamine (both endogenous and exogenous) appears to have an important role in an immediate response (EPR) to allergen in the nasal mucosa that is different from the response in the skin. The role of histamine, probably originating from basophils rather than from mast cells in the late inflammatory response, is not clear. Histamine's role in inducing sneezing is more apparent than in affecting nasal rhinorrhea and congestion, which are controlled by other agents, such as vasoactive intestinal peptide (VIP), substance P, and other mediators such as PGD₂ and leukotrienes.

Whether histamine arises endogenously from mast cells or is derived exogenously from histamine spray, the

TABLE V. Comparative placebo-controlled studies of antihistamines and their efficacy in the treatment of SAR

Reference	Study type	Patients (n)	Drug	Duration (wk)	Symptom control*
Davies et al. ³⁴	DB, PC	487	C 10 mg AM C 10 mg PM T 60 mg BID	8	C > T (eye symptoms)
Bousquet ³⁵	DB, PC	452	L 10 mg OD Ast 10 mg OD	2	L > A > P
Kemp et al. ³⁶	DB, PC	397	T 60 mg BID Chl 4 mg TID	1	T = Chl > P
Dockhorn et al. ³⁷	DB, PC	321	L 10 mg OD Cl 1 mg OD	2	L = Cl > P
De Carpio et al. ³⁸	DB, PC	317	L 10 mg OD T 60 mg BID	2	L = T > P
Kemp et al. ³⁹	DB, PC	313	L 10 mg OD Cl 1 mg OD	2	L = Cl > P
Siegal et al. ⁴⁰	DB, PC	271	L 5-10 mg OD Chl 2-4 mg OD	2	L = Chl > P
Reed et al. ⁴¹	DB, PC	270	C 10 mg OD Ast 10 mg OD	33	C = A > P
Horak et al. ⁴²	DB, PC	256	L 10 mg OD T 60 mg BID	2	L = T > P
Alexander et al. ⁴³	DB, PC	241	C 10 mg OD L 10 mg OD	2	C = L > P
Buckley et al. ⁴⁴	DB, PC	215	T 60 mg BID Chl 4 mg TID	1	T = Chl > P
Backhouse and Rosenberg ⁴⁵	DB, PC	138	T 60 mg BID	6	T = Chl > P
Backhouse et al. ⁴⁶	DB, PC	136	Chl 4 mg TID T 60 mg BID Chl 8 mg BID	1	T = Chl > P
Oei ⁴⁷	DB, PC	65	L 10 mg OD Ast 10 mg OD	2	L > A > P
Skassa-Brociek et al. ⁴⁸	DB, PC	64	L 10 mg OD Meq 5 mg BID	2	L = Meq > P
Brandon and Weiner ⁴⁹	DB, PC	60	T 20 mg TID Chl 4 mg TID	1 (ave)	T > Chl > P
Brostoff and Lockhart ⁵⁰	DB, PC	60	T 60 mg BID Chl 8 mg BID	2	T = Chl > P
Grossman et al. ⁵¹	DB, PC	53	C 10 mg OD T 60 mg BID	4	C = T > P

Meq, Mequitazine; ave, average. Other abbreviations as in Table II.

*The > sign refers to the first antihistamine being more effective in the suppression of the commonly measured symptoms of allergic rhinitis (sneezing, itch, etc.) with respect to the second antihistamine. The = sign refers to the two antihistamines not differing with respect to the above parameters.

mechanism underlying the immediate nasal response and the pharmacologic actions of the antihistamine is similar. It is known that antihistamines exert their pharmacologic effects by competitive antagonism of histamine for H₁-cellular receptors—specifically, the H₁ receptors present on smooth muscles, nerve endings, and glandular cells. However, additional mechanisms of action may contribute to their clinical efficacy. These additional actions cannot be predicted from the results of the histamine-induced skin wheal and flare test.

Itching and sneezing (from sensory nerve stimulation) are effectively suppressed by antihistaminic blockade of H₁ receptors on nasal sensory nerves. Although antihistamines block rhinorrhea as a result of histamine-induced increases in vascular permeability, they may not

affect increased secretion caused by parasympathetic activation of nasal mucosal glands and are less effective when it comes to the control of congestion. It appears that mediators other than histamine are important in eliciting this symptom.

COMPARISONS OF ANTIHISTAMINES BY MEANS OF THE HISTAMINE-INDUCED SKIN WHEEL AND FLARE

How do various antihistamines compare using this test system?

Table II summarizes the results of 13 comparative trials of antihistamines in the suppression of cutaneous histamine-induced wheal and flare. Most drugs were shown to be better than placebo; however, Table II

TABLE VI. Direct comparative studies (no placebo) of antihistamines and their efficacy in the treatment of SAR

Reference	Study type	Patients (n)	Drug	Duration (wk)	Symptom control*
Davies ⁵²	Para	401	C 10 mg AM C 10 mg PM T 60 mg BID	8	C = T
Backhouse et al. ⁵³	DB, Para	285	C 10 mg OD T 120 mg OD	1	C = T
Haltom et al. ⁵⁴	SB	160	C 10 mg OD T 60 mg BID	1	C = T
Lockey et al. ⁵⁵	SB, Para	160	C 10 mg PM T 60 mg BID	1	C ≥ T
Caiaffa et al. ⁵⁶	DB	136	C 10 mg OD T 120 mg OD	1	C = T
Harcup et al. ⁵⁷	DB, Para	115	C 10 mg OD Ast 10 mg OD	4	C = A
Herman et al. ⁵⁸	DB	108	C 10 mg OD L 10 mg OD	2	L = C
Olsen et al. ⁵⁹		105	L 10 mg OD T 120 mg OD	3	L = T
Rijntes et al. ⁶⁰	DB	105	C 10 mg OD Ast 10 mg OD	2	C = A
Tjwa et al. ⁶¹	DB, Para	96	C 10 mg OD L 10 mg OD	2	L = C
D'Amato et al. ⁶²	DB, Para	51	C 10 mg OD T 120 mg OD	1	T ≥ C
Rossi and Bertoni ⁶³	DB, Para	30	C 10 mg OD Ast 10 mg OD	3	C = A
Katellaris ⁶⁴		28	L 10 mg OD Az 1 mg BID	2	L = Az

Az, Azatadine. Other abbreviations as in Tables II and IV. Symbols as in Table V.

shows that there is considerable variability in suppression of the histamine-induced wheal and flare response. From these results it might be concluded that all antihistamines are not equally suppressive of the cutaneous histamine-induced wheal and flare response. In particular, cetirizine appears to be more suppressive than others in controlling this reaction.

How do antihistamines compare in clinical efficacy in the treatment of chronic idiopathic urticaria?

Urticaria is a common allergic disease which (along with the related disease, angioedema) affects up to 20% of the population. Physically, it consists of red, well-defined lesions that are often raised and pruritic. This disease may be acute or chronic in nature and is caused by a variety of physical factors (i.e., temperature, pressure, water), food allergies, drug reactions, endocrine diseases, and infections, but it can be idiopathic. Idiopathic urticaria can recur repeatedly for months to years in contrast to acute urticaria, which resolves over a period of hours and recurs only if the inciting stimulus is encountered again.

The mast cell has been ascribed an important role in the pathologic mechanism of CIU because it is present in increased numbers in the skin of these patients.⁷ PGD₂, LTC₄, LTD₄, platelet-activating factor, and bra-

dykinin contribute to the vasodilation and edema. PGD₂ is a vasodilator, and LTC₄ and LTD₄ mediate increased vascular permeability. Histamine, however, acting through its H₁ receptor, can mediate all three components of urticaria, namely pruritus, vascular permeability, and vasodilation.

Long-term medical therapy is commonly required for patients with CIU, and H₁-antihistamine therapy represents a major therapeutic option.⁸ Table II shows that various antihistamines exhibit differing degrees and durations of suppression of histamine-induced skin wheal and flare. If this test were a very reliable indicator of the global antiallergic effects of antihistaminic drugs, a rank order of symptom control should be apparent among the various antihistamines, and cetirizine also should demonstrate greater control of the symptoms and signs of CIU. However, this does not appear to be the case.

Tables III and IV summarize the results of clinical studies comparing the efficacy of various antihistamines in CIU. In seven trials involving cetirizine, 3 (43%) demonstrated equivalence with the active comparator, 3 (43%) showed cetirizine to be more effective than its comparator, and 1 (14%) showed the comparator to be more effective than cetirizine. This finding contrasts with reports of the histamine-induced wheal and flare trials, where 8 (66%) of 12 showed cetirizine to be more suppressive than the comparative antihistamines. There-

fore cetirizine, which strongly suppresses the cutaneous histamine-induced wheal and flare reaction, demonstrates no relevant clinical superiority over other antihistamines in the treatment of CIU. The apparent comparative ratings of the various antihistamines in suppressing the histamine-induced wheal and flare reaction are not maintained when comparing the clinical efficacy outcomes; these antihistamines are essentially therapeutically equivalent.

How do the antihistamines compare in clinical efficacy in the treatment of seasonal allergic rhinitis?

The results of comparative trials with various antihistamines in the treatment of SAR are noted in Tables V and VI. In trials with placebo-controlled comparisons, 14 (78%) of 18 demonstrate equivalent clinical efficacy of the comparative medications. In the nonplacebo-controlled trials, 11 (85%) of 13 studies show clinical equivalence. For the other trials, comparative results were variable among the antihistamines.

DISCUSSION

In this review, we have examined the mechanisms that underlie the responses to histamine and to allergen challenges in the skin and the nasal mucosa. The claimed predictive utility of the cutaneous histamine-induced wheal and flare test is based on an assumption that the degree of suppression of the cutaneous histamine-induced wheal and flare response reflects the global antiallergic histamine activity of antihistaminic drugs and supports comparative therapeutic claims. Although histamine occupies an important role in the allergic response of the skin, other mediators and cells are equally (or more) important. The epicutaneous injection of pharmacologic doses of histamine results in a wheal and flare reaction that is overtly similar to the normal skin EPR that follows allergen challenge. It is important to realize, however, that the histamine-induced wheal and flare reaction involves neither mast cell degranulation nor activation of the complex cascade of cellular events that result in the LPR. From a purely functional point of view, therefore, the histamine-induced wheal and flare is an incomplete reflection of the natural cutaneous and nasal mucosa responses to allergens.

As shown above, the skin and the nasal mucosa differ fundamentally from a physiologic standpoint and in their responses to histamine and allergen challenges. A comparison of the efficacy outcomes seen in the treatment of CIU and SAR with the results of cutaneous histamine-induced wheal and flare studies indicates that this skin test is an incomplete reflection of the antiallergic therapeutic effects of antihistamines in the nose and even in the skin itself. These divergences question the reliability of this test as a predictor of global antiallergic effects. The results of this literature review were recently confirmed in a clinical study in which loratadine and cetirizine exhibited the same therapeutic effect after nasal

challenge with grass pollens but reacted differently after skin tests with allergen or histamine.⁶⁵ We conclude that significant structural, functional, and response differences between the skin and the nasal mucosa (neural, vascular, cellular) make it inappropriate to apply the results of cutaneous histamine-induced wheal and flare tests in predicting the relative therapeutic utility of antihistamines in clinical allergy.

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