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Effect of H₁-receptor blockade on late cutaneous reactions to antigen: A double-blind, controlled study

C. Warren Bierman, MD,* David Maxwell, MD,** Ed Rytina, MD,***
Michael B. Emanuel, PhD,**** and Tak H. Lee, MD, FRCP**
Seattle, Wash., and London, England

This study is of the effect of the blockade of histamine H₁ receptors by a long-acting antihistamine on the immediate and late clinical response to antigen (Ag) and on the recruitment of eosinophils in the late-phase cutaneous reaction. Ten adult volunteers with late-phase reactions to the intradermal injection of either Dermatophagoides pteronyssinus or Phleum pratense (timothy) pollen performed a double-blind, crossover study. Each volunteer took astemizole, 10 mg, or identical placebo, daily for 2 weeks. Ag in the concentration that induced a late reaction in the screening visit was injected intradermally at the end of each drug period. The early reaction was measured serially for 30 minutes and the late reaction at 4 and 6 hours. Biopsies of the Ag and control sites were also performed at 6 hours. After a 6-week washout period, subjects then took the opposite medication for 2 weeks and returned for skin testing and biopsy. Skin testing demonstrated that astemizole inhibited the immediate response to both histamine and allergen but had no effect on the late response at 4 hours and at 6 hours. Biopsy specimens revealed no significant effect on eosinophil recruitment at 6 hours. We conclude that histamine H₁-receptor blockade has no effect on the late cutaneous reaction to Ag. (J ALLERGY CLIN IMMUNOL 1991;87:1013-9.)

From the *Division of Allergy, Department of Pediatrics, University of Washington, Seattle, Wash., **Departments of Allergy and ***Pathology, Guy's Hospital Medical School, London, England, and the ****Janssen Research Foundation, United Kingdom.

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Reprint requests: C. Warren Bierman, MD, Clinical Professor of Pediatrics, University of Washington, 4540 Sand Point Way NE, Seattle, WA 98105.

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When a sufficient quantity of specific Ag is injected into the forearm of an allergic subject, an immediate wheal and flare appears within 10 to 20 minutes. Often, it is followed by a substantially larger area of induration some 4 to 12 hours later. The larger the quantity of Ag injected, the larger the diameter of the wheal-and-flare response and the larger the late cutaneous allergic response. A similar late-phase reaction to nasal Ag challenge and bronchial challenge occurs in many subjects with allergic rhinitis and/or asthma.

Such dual skin reactions have clearly been demonstrated to be related to the isolated involvement of allergen-specific IgE.¹ Furthermore, Ag-stimulated sites are associated with a second peak of histamine and a marked increase in EOSs and basos with mediator release apparently being derived from basos.² In contrast, Dolovich et al.³ found that the intracutaneous injection of codeine, a known liberator of mast cell mediators in both normal subjects and patients with allergy, elicited a large wheal-and-flare response at 15 minutes but not a late reaction at 6 hours, whereas the use of specific allergen in the allergic subjects did elicit a late reaction.³ These authors proposed three alternatives to explain this dichotomy: (1) a possible qualitative or quantitative difference in the pattern of release/activation of mast cell mediators, (2) a biphasic liberation of mediators to the IgE response that might progress to a late response,⁴ and (3) that late allergic responses require IgE-dependent effects on cell types other than mast cells. Activated EOSs and eosinophilic basic protein were found in both skin, after late reactions to Ag, and in bronchial secretions, after late reactions to bronchial Ag challenge or acute asthma. Since cetirizine, an H₁ antihistamine, has been demonstrated to have clear-cut inhibitory effects on EOS migration both in vivo⁵ and in vitro,⁶ the present study was performed to observe if inhibition of EOS recruitment is a general property of H₁ blocking agents or whether the effect of cetirizine is independent of its antihistamine action.

This study focused specifically on recruitment of EOSs, since EOSs are prominent in late reactions in both skin and airways. In the airways, eosinophilic inflammation is correlated with severity of asthma.⁷ Therefore, any agent that minimizes recruitment of these cells to late reactions has the potential to minimize the deleterious effect of EOS granule-derived proteins in the late reaction.

MATERIAL AND METHODS

Subjects

Ten volunteers who were atopic with both early and late reactions to timothy pollen or house dust mite Ag admin-

Abbreviations used

Ag:	Antigen
PBS:	Phosphate-buffered saline
baso:	Basophils
EOS:	Eosinophils
HPF:	High-power field

istered intradermally were invited to participate. The number of volunteers needed was determined in advance. Statistical analysis of previous studies by the Janssen Research Foundation statisticians indicated that active treatment should inhibit immediate wheal-and-flare reactions by 50% and that with 90% power in two-sided tests at 5% significance level, a minimum of eight volunteers to complete the study was required to establish significance (Emanuel MB, O'Donovan M. Personal communication [Janssen Research Foundation LTD]). All volunteers signed informed consent that had been approved by the Guy's Hospital Ethical Committee.

Skin tests

AgS for skin testing were kindly supplied in lyophilized 1 ml aliquots of either *Dermatophagoides pteronyssinus* or *Phleum pratense*, 1 million SQ units per milliliter.⁸ The lyophilized Ags were kept refrigerated until use, and the concentrated Ags were diluted monthly. Dilutions were prepared consisting of 12,000 SQ units per milliliter (strong solution), 1200 SQ units per milliliter (intermediate solution), or 400 SQ units per milliliter (weak solution) and were used within 48 hours of preparation. Histamine phosphate solutions consisting of 0.1, 0.3, 1, 3, and 10 mg/ml of PBS were prepared by the Guy's Hospital Pharmacy. PBS was used as a negative control. The second series of skin tests were performed at least 14 days after the first set and the third set 10 weeks after the qualifying skin tests. No pollen tests were performed during the pollen season.

Cutaneous biopsies

The site was first anesthetized with 1% lidocaine (without adrenaline) that was injected around the periphery of the biopsy site. The biopsies were performed at the Ag injection sites with a 4 mm punch in all subjects 6 hours after the intradermal injection. In addition, each subject had a biopsy of the saline control site taken from uninvolved skin coincident with either the first or second biopsy of the Ag site. The biopsy specimens were placed in 10% formal saline for 24 hours, embedded in paraffin, and stained with hematoxylin and eosin. Sections were coded and read in a blind fashion for EOSs by a physician (E. R.) who had no involvement with the clinical portion of the study. The number of extravascular EOSs in each biopsy specimen was counted per 10 HPFs (Olympus BH-2 microscope, Olympus WHK 10 x/20L eyepiece, 1.25 x 10, and an Olympus SPlan, 40.0.70 160/0.17 objective, Olympus Corp., Lake Success,

TABLE I. Experimental design

Visit	1		2						3		4
Weeks	0	1	2	3	4	5	6	7	8	9	10
Histamine PP	x		x						x		x
Intradermal tests											
PBS	x		x								x
Ag	x		x								x
Measure wheal and flare											
15 and 30 min, 40 and 6 hr	x		x								x
Biopsy control site											
Subjects 1, 3, 5, 7, 9			x								
Control site											
Subjects 2, 4, 6, 8, 10											x
Ag site			x								x
Medication randomized	Medication period 1				Wash out period				Medication period 2		
	Active or placebo								Placebo or active		

N.Y.) of papillary and middermis covering an area of 1.0 mm².

The EOS counts were performed on two occasions. The correlation coefficient was >0.8. The reproducibility of the measurement of the late response in individual subjects can be computed from the placebo-treatment day and active drug-treatment day.

Medication

Astemizole, 10 mg, or identical matching placebo was supplied by Janssen Pharmaceutical, Ltd. This medication was randomized by the Guy's Hospital pharmacist. Astemizole was administered in this dosage because 10 mg is maximum dose approved by the Food and Drug Administration in the United States and by the Committee on Safety of Medicine in the United Kingdom.

Procedure (Table I)

On the subject's arrival in the clinic, the following prick skin tests were performed: (1) *allergen*: concentrated grass pollen and house dust mite Ag, (2) *histamine*: 0.1, 0.3, 1, 3, and 10 mg/ml, and (3) *control*: PBS. The mean diameter of the wheal and flare were recorded at 15 and 20 minutes after each test. Ag was injected intracutaneously into the nondominate supinated forearm. The concentration of the Ag used was determined by the size of the reaction to the prick tests on the qualifying day. If the prick test wheal was <8 mm in diameter, 0.02 ml of the strong solution was administered. If the prick test wheal was between 8 and 10 mm, 0.02 ml of the intermediate strength solution was administered. If the prick test wheal was >10 mm, 0.02 ml

of the weak strength solution was administered. A buffered saline control was injected at a site 7 cm or larger below the Ag injection site. If at 6 hours the late response was <5 mm, the next stronger Ag was used for the remainder of the study, whereas, if at 6 hours, the late response was >80 mm, the next weaker strength Ag was used for the remainder of the study. The subjects were then administered either astemizole, 10 mg per day for 14 days, or a matching placebo. On the fourteenth day, the subject returned for histamine titration by skin prick test and the intradermal injection of Ag, as determined by the initial visit, and a PBS control was injected 7 to 9 cm distal to the allergen-injection site. Mean wheal-and-flare diameters were measured 10, 15, 20, and 30 minutes after the skin test, and the size of the late reaction was measured at 4 and 6 hours after injection. After a 6-week washout period, subjects returned for histamine titration to be certain that their skin reactivity to histamine had returned to normal. They were then administered the second medication to be taken daily for the following 2 weeks, and at the end of this period, they returned for the procedures noted in visit 2. Six hours after each injection, biopsies were performed at the Ag-injection sites. Half the subjects had biopsies of the control site performed on the second visit and the other half, on the fourth visit.

Statistical analysis

Comparisons of the mean wheal size at each time point after pretreatment with placebo or astemizole was performed with repeated measure analysis of variance for paired data.

TABLE II. Clinical characteristics of the 10 subjects studied and the Ag responsible for the skin tests with the diameter of the immediate and late reaction after intradermal allergen testing on qualifying day

Patient	Age (yr)	Sex	Ag	Skin reaction (mm)	
				Immediate	Late
1	23	F	Grass	9 × 7	50 × 50
2	22	F	Grass	10 × 17	30 × 20
3	23	M	Grass	18 × 18	60 × 45
4	43	M	<i>Dpt</i>	20 × 12	70 × 45
5	48	F	Grass	18 × 15	50 × 75
6	61	F	Grass	14 × 10	10 × 12
7	47	M	Grass	25 × 25	80 × 70
8	63	M	<i>Dpt</i>	10 × 15	15 × 15
9	20	M	Grass	15 × 15	10 × 10
10	24	F	Grass	9 × 17	82 × 95

Dpt, Dermatophagoides pteronyssinus.

Comparison of the number of EOSs per 10 HPFs migrating to the site of injection after pretreatment with placebo or astemizole was performed with the paired Student's *t* test.

RESULTS

Clinical

All ten subjects completed the study. The characteristics of the subjects are noted in Table II. The results of the skin tests are noted in Table III. There was a statistically significant difference in the size of the histamine wheal and flare at the end of the active-treatment and placebo-treatment periods ($p = 0.004$). A statistically significant difference was also noted in the immediate reaction to Ag at 20 minutes between active and placebo treatments ($p = 0.02$). Astemizole thus decreased the size of the histamine wheals and the size of the immediate skin test reactions. At 4 and 6 hours, however, there was no difference in the mean diameter at the Ag-injection site at the end of the astemizole-treatment period as compared to the end of the placebo-treatment period. Thus, H₁-receptor blockade had no effect on the late cutaneous reaction to Ag.

Biopsies

The numbers of EOSs infiltrating the biopsy sites are noted in Table IV. In the biopsy specimens of the control subjects, only three subjects had any EOSs (one, two, and three cells each) in areas injected with PBS. In the remaining subjects, EOSs were distinctively absent. In the biopsy specimens of the sites injected with Ag, a substantial number of EOSs were found infiltrating the cutaneous tissue 6 hours after Ag injection. No significant differences were ob-

served in biopsy specimens obtained after 14 days of astemizole therapy as compared to 14 days of placebo therapy.

DISCUSSION

Recent studies by Frew and Kay⁹ have indicated that late-phase skin reactions to aeroallergens can be induced in all subjects who are allergic to these Ags. In their study with both *D. pteronyssinus* and mixed grass pollen, they demonstrated a dose-response relationship between the concentration of Ag used and the size of the late-phase response. By using the largest dose of Ag (30 biologic units),¹⁰ they were able to induce a late-phase response in all 20 unselected subjects with the late reaction consisting of induration of >5 mm in diameter at the site of injection. By contrast, histamine skin reactions of a similar size resolved fully in 2 hours, and up to 100 biologic units could be injected into a nonatopic subject's skin without any local reaction.

The morphology of late cutaneous reactions to Ag has been studied in depth. Ag injection frequently stimulates a dense cellular infiltrate.¹¹ EOSs are particularly prominent, beginning to appear in the peri-appendigeal area of the skin 20 minutes after Ag injection and appearing in increasing concentration with peak infiltrations 240 minutes after Ag injection.¹² EOSs subsequently decrease in concentration in biopsy specimens obtained at 48 hours.¹³ Both CD3⁺ and CD4⁺ T-lymphocytes have also been observed in significantly increased numbers at allergen-challenged sites,¹⁴ whereas the number of CD8⁺ cells are not significantly different from the number found in control biopsy specimens. Mononuclear cells arrive at allergic reaction sites within 6 hours and persist for

TABLE III. Diameter of wheals or induration $\pm$ standard deviation after histamine (prick puncture, 10 mg/ml) at 20 minutes and Ag intradermal injection during astemizole- and placebo-treatment periods at 20 minutes and 4 and 6 hours

	Histamine*	Ag		
		20 min	4 hr	6 hr
Placebo (mean diam wheal) (mm) $\pm$ SD	6.11 $\pm$ 1.47	13.4 $\pm$ 2.03	27.7 $\pm$ 14	29.4 $\pm$ 17.3
Astemizole (mean diam wheal) (mm) $\pm$ SD	4.2 $\pm$ 1.67	8.85 $\pm$ 3.87	22.4 $\pm$ 16	25.1 $\pm$ 17.9
Significance of difference	0.0042	0.02	0.18	0.27

Since a substantially higher concentration of histamine was used in the study than usually used as a positive control, the wheal size in the volunteers receiving astemizole is larger than it would have been with the usual concentration of 2 mg/ml.

at least 48 hours, at which time mononuclear cell types predominate. The significance of this finding is not clear at the present time.

The accessibility of the skin has made it an attractive model in which to study late-phase responses. Chemical mediators and cell morphology have been assayed in skin-blister fluid samples obtained after allergen skin testing in patients with late cutaneous reactions. This technique of sampling creates a skin blister with a negative pressure of 200 mm of mercury.¹⁵ Histamine in the blister fluid has a biphasic response, is predominant during the early phase of the wheal-and-flare reaction, and rises again 6 to 7 hours² after Ag injection. Thromboxane B₂ content increased with the development of the late-phase reaction and reached a peak 6 hours after skin testing. By contrast, patients without late reactions had no increase in thromboxane levels. Less clear-cut is the finding of platelet-activating factor since it is also present in skin-blister fluid from normal skin.¹⁶

The late-phase reaction, originally noted in the skin, has since been observed in the lung and nose. In the lungs, the late-phase response often begins 3 hours after exposure but can also begin as late as 6 hours after Ag challenge and is characterized by a fall in FEV₁. In the skin, mediator release reaches a peak at 6 hours when inflammatory cells begin to accumulate and is characterized by induration. As in the airways, there is a dual peak release of mediators.¹⁷ Histamine release continues to 12 hours after challenge, and prostaglandin D₂ occurs somewhat later than histamine. Basos and EOSs accumulate in skin-chamber models with as much as a twentyfold increase as compared to the increase in control subjects. EOSs were frequently noted to have a vacuolated appearance consistent with "activated" hypodense EOSs. Such cells

TABLE IV. Number of EOSs per high-power field in biopsy specimens 6 hours after injection of PBS (control) or Ag after placebo or astemizol administration

	EOSs		
	Control (after PBS)	Ag	
		Placebo	Astemizole
Subject			
1	1	5	3
2	0	18	8
3	0	0	7
4	0	29	66
5	0	9	25
6	0	3	12
7	2	115	165
8	0	11	42
9	3	68	39
10	0	55	89
Mean $\pm$ SD	0.6 $\pm$ 1.02	31.3 $\pm$ 35.3	45.6 $\pm$ 47.8

p, Not significant (placebo versus astemizole).

have been demonstrated to have increased metabolic activity with increased surface markers for IgE, IgG, and C3b.¹⁸ In addition, EOS cationic proteins may play a direct role in enhancing baso and mast cell activation.¹⁹

Late-onset pulmonary responses also occur after inhalation of pollen Ag and appear to be as severe as the early bronchospastic responses but persist for longer duration. In general, the similarity of timing between late-onset skin and bronchial responses would suggest a strong relationship between these phenomena, although there is a dichotomy between

factors that predict the intensity and degree of the reaction.²⁰

The effect of anti-inflammatory steroids on the late reaction have been studied in several studies. In 1976, Poothullil et al.²¹ demonstrated inhibition of late cutaneous allergic responses induced by antiserum to human IgE. Subsequently, Dolovich et al.³ studied three subjects with angioedema who had late cutaneous reactions to histamine or to codeine phosphate injected intradermally. Subjects responded dramatically clinically to prednisone, which also blocked this late reaction. Pippcorn et al.,²² using the skin-chamber models, demonstrated the same selective late-phase suppression of histamine secretion as well as blocking the influx of EOSs and basos into the skin chamber by dexamethasone. Similar late-phase suppression of mediator release after Ag challenge by prednisone has been documented in nasal mediator release.²³ Although it would have been of interest to include a positive control with steroids in this study, the ethics committee would not permit a fourth skin biopsy.

In the present study, we examined the effect of a unique H₁-receptor blocker versus placebo on the late cutaneous response to Ag. Astemizole has a unique affinity only for H₁ receptors and hence is free from "atropine-like" effects. Gendreau-Reid et al.²³ have demonstrated by histamine skin titration that the dosage used is sufficient to achieve a high degree of histamine blockade.

Astemizole significantly decreased the response to histamine prick tests and the initial wheal and flare induced by an intradermal skin test to either timothy pollen or *D. Pteronysinus* extract. The fact that it did not inhibit the histamine wheal to a greater extent was probably related to the concentration of histamine that we used, 10 mg/ml, rather than the usual 2 mg/ml used in the United States. It did not alter the clinical appearance of the late response to Ag at either 4 or 6 hours or alter the recruitment of EOSs at 6 hours in the skin biopsy specimens. The results of this study are identical to results of Atkins et al.¹³ who studied EOS recruitment by biopsy specimen before and after 100 mg of hydroxyzine daily.

These results are in marked contrast to recent studies. One used the Rebuck skin window technique²⁴ and the other study used the blister-fluid technique.²⁵ In the first study, the percentage of EOSs in the skin window was 6.6% with cetirizine and 16.9% with placebo ($p < 0.01$). Charlesworth et al.,² using the suction-induced blister technique with a cutaneous chamber, found that 20 mg of cetirizine per day significantly inhibited the infiltrate of EOSs produced by an allergic stimulus. These authors measured cellular

recruitment directly by counting the leukocytes in the chamber fluid 6 to 8 hours after the onset of the reaction and noted a 65% to 83% inhibition of EOS accumulation.

There are several possible explanations for the discrepancy between the present study and previous studies on cetirizine. First, the trauma of creating a skin window or a blister chamber might induce EOS recruitment that is blocked by an H₁-receptor antagonist. Suction of blister fluid from the skin of some nonallergic subjects can induce plasma exudation and produce vasoactive mediators. Elevated levels of kallikrein, thromboxane B₂, and platelet-activating factor have been found in blister fluid of some normal subjects.¹⁶ As previously noted, the injection of blister fluid from these subjects can induce late cutaneous reactions in other normal subjects. It would be of interest to assess whether cetirizine inhibits EOS infiltration, as evaluated by both blister-fluid/skin-window technique as well as biopsy specimen, in the same subjects after Ag injection. Secondly, cetirizine might inhibit EOS recruitment by Ag in the skin blister fluid and Rebuck skin window models via a mechanism other than its anti-H₁ activity. Against this concept is the fact that Atkins et al.¹³ treated volunteers with hydroxyzine with a dose of 100 mg/day for 5 days and found no inhibition of EOS recruitment in biopsy specimens for 6 hours after Ag injection. Since 45% to 60% of hydroxyzine is converted to cetirizine as its major metabolite, these subjects would have received 45 to 60 mg of cetirizine daily before their biopsy with no effect on EOS recruitment. This finding would suggest that the difference between these studies would be one of technique rather than a difference between drugs.

We have demonstrated that the administration of astemizole at a dose that produced significant inhibition of both histamine and Ag-induced early responses does not affect EOS recruitment in the Ag-induced late-phase reaction. This suggests that blockade of H₁ receptors per se is insufficient to prevent the eosinophilia of the late-phase reaction in the skin. We cannot exclude the possibility that astemizole would prevent or modify EOS recruitment and late reactions after Ag challenge in the respiratory tract. This possibility will require future study.

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