

Effects of loratadine on anti-IgE-induced inflammation, histamine release, and leukocyte recruitment in skin of atopics

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The aim of this study was to assess the ability of the H_1 -receptor antagonist loratadine to modify anti-IgE-induced cutaneous wheal-and-flare and late-phase reactions (WFR and LPR), as well as histamine release and leukocyte accumulation in skin chambers. For this purpose, 10 atopics with allergic rhinitis were entered into a double-blind crossover study in which they received either placebo or loratadine (20 mg/day orally) for 8 days separated by a 7-day washout period. Blisters were induced on both forearms on day 7 of each treatment period, and were unroofed on day 8 and covered with plastic skin chambers. Chamber fluids were collected during 7 h after 1-h incubation with anti-IgE or control IgG. Intradermal challenge with histamine and anti-IgE was performed at the same occasion. As compared to placebo treatment, loratadine inhibited the immediate WFRs to anti-IgE by 35% (wheal) and 65% (flare), respectively ($P < 0.01$), and corresponding reactions to histamine challenge by 50% and 70% ($P < 0.001$), respectively. Moreover, the initial phase (0–2 h) of the LPR induced by anti-IgE was attenuated by up to $\approx 60\%$ ($P < 0.001$) during loratadine treatment. Thereafter, no inhibition of the LPR was observed. The magnitude and time course of histamine release into skin chambers was virtually the same after loratadine and placebo treatment, with a peak during 0–1 h and a progressive decline during the following 2 h. Accumulation of α_2 -macroglobulin, reflecting extravasation of large plasma proteins, also peaked during the first hour and was unaffected by loratadine during the 8-h observation period. Moreover, loratadine did not reduce the anti-IgE-induced recruitment of eosinophils or other subtypes of leukocytes. Altogether, loratadine inhibited both the WFRs to histamine and anti-IgE and the initial phase of the IgE-mediated LPR. However, loratadine did not express anti-inflammatory activity with respect to mast-cell mediator release or leukocyte recruitment. The latter findings are in contrast to the action of loratadine in allergic rhinitis and conjunctivitis, suggesting that the actions of loratadine may be organ specific and that the effects of loratadine cannot always be extrapolated from one tissue to another.

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The first generation of antihistamines act on both central and peripheral H_1 -receptors, thereby commonly causing adverse effects such as dry mouth and sedation. The second generation of H_1 antihistamines, demonstrated to reduce allergic reactions in skin, nasal, and lung as well as ocular challenge studies (22), act more selectively in the periphery, probably because of higher selectivity at H_1 -receptors and because they poorly cross the blood–brain bar-

rier (21). Interestingly, some of these compounds (loratadine, cetirizine, astemizole) have been reported to inhibit allergic inflammation in different tissues via mechanisms apparently unrelated to histamine antagonism; i.e., their effects have been ascribed to inhibition of effector mechanisms such as mast-cell mediator release, increased vascular permeability, and eosinophil recruitment (1, 3, 7, 8, 20). Moreover, as indicated in studies of allergen-

induced late-phase reactions (LPRs) and eosinophil recruitment in human skin, these antihistamines appear to have different profiles of action. For example, in contrast to terfenadine, astemizole, and first-generation H_1 -receptor antagonists, cetirizine has been shown to inhibit late cutaneous eosinophil recruitment (2, 5, 6, 10, 17). Furthermore, while cetirizine and astemizole have little or no inhibitory effect on the edema/induration of LPRs, terfenadine clearly inhibits this LPR component (6, 16, 23). With respect to loratadine, this antihistamine has been shown to inhibit allergen- and histamine-induced wheal-and-flare reactions (WFRs) (25); however, the potential of loratadine to modify other aspects of IgE-mediated skin inflammation has not been evaluated. Therefore, we performed this study in atopic subjects to examine whether or not loratadine can modify anti-IgE-induced LPRs and/or histamine release and leukocyte recruitment into skin chambers. Anti-IgE challenge was used because it is a safe and reproducible alternative to cutaneous allergen provocation (11, 26), and the choice of atopic patients was based on previous observations that significant dermal eosinophil recruitment in response to anti-IgE occurs in atopic, but not in healthy, subjects (14).

Material and methods

Patients

Ten atopic patients, five men and five women aged 21–33 years (mean 26) with a history of seasonal allergic rhinitis, mean total IgE of 165 kU/l (44–570), and positive prick test and RAST (2–5) to birch and/or timothy pollen, were recruited. All subjects in the study were drug-free, and tested negative to intradermal injection of normal goat IgG and had negative RAST to goat epithelium. All subjects gave their informed consent to participate in the study, which was approved by the ethical committee of the Karolinska Hospital.

Loratadine and placebo treatment

The study was performed outside the pollen season in a double-blind, two-way, crossover manner, comparing a 1-week pretreatment with loratadine (Schering-Plough AB, Stockholm, Sweden, 20 mg) with placebo (Schering-Plough AB), given as identical tablets each morning. Each subject received the two treatments in a randomized order with each laboratory visit separated by a 7-day washout period. Half of the patients received loratadine during the first treatment period and the other half placebo. Skin tests and skin chamber experiments were performed in the morning of day 8 of each treatment period, beginning 1 h after intake of the respective tablet.

Reagents for skin testing

Affinity-purified goat antihuman IgE (epsilon-chain specific) and chromatographically purified normal goat IgG were obtained from AB Kemila-Preparat (Sollentuna, Sweden). The lyophilized antibodies were reconstituted in sterile PBS and dialyzed against PBS for 24 h. The antibodies were then passed through a Millipore filter (0.22 μ m), analyzed for protein content according to Bradford (4), diluted to 0.1 mg/ml (= titer 1:10) in sterile PBS, divided into aliquots, and stored frozen at -20°C . The LPRs induced by the anti-IgE developed in a dose-dependent manner, and the concentration of anti-IgE chosen for intradermal injection (1:100) was found to cause distinct, continuously growing LPRs peaking at 6–10 h in five subjects (not shown).

Histamine phosphate (British Drug House, Poole, UK) was dissolved in sterile PBS at a concentration of 60 μ M and passed through a Millipore filter (0.22 μ m).

Skin chambers

Skin blisters were induced on the volar aspect of each forearm with a negative pressure cutaneous suction chamber system (Electronic Diversities, Finksburg, MD, USA). The suction chamber was placed on a cleaned skin area, followed by continuous gentle suction (300 mmHg) and heating (39°C) for 2–3 h until a complete blister (9 mm in diameter) was formed. The blisters were covered overnight with a plastic eye chamber, and the next morning the blisters were aseptically unroofed. A transparent sterile adhesive plastic film (Tegaderm, 3M Pharmaceuticals, Loughborough, UK) with a circular hole was applied around the denuded blister base, staying 3 mm away from the blister area. The film was used to protect intact skin from possible irritation by a cutaneous adhesive (Skin Bond Cement, Largo, FL, USA). The Skin Bond Cement was applied around the bottom edge of sterilized open-bottom plastic skin chambers (volume $\approx$ 1 ml) which were placed over the unroofed blisters and secured by tape. The chambers were then washed four times with sterile PBS containing 30 IE/ml heparin. A volume of 150 μ l anti-IgE (1:10 in PBS/heparin) was infused into one chamber, while the contralateral control chamber received normal goat IgG (1:10 in PBS/heparin). After 1 h of incubation, the chambers were filled with PBS/heparin, and the fluid was carefully aspirated and reinstalled two times to allow a complete collection of exudate. The chambers were then refilled with PBS/heparin, and chamber contents were removed hourly for the next 3 h. This was followed by incubation with PBS/heparin for 4 h (4–8 h after start of challenge) before final removal.

All aliquots were spun at 300 g for 5 min at 4°C. The supernatants were immediately frozen and stored at -70°C for up to 1 week before analysis of histamine and α_2 -macroglobulin content. The cell pellets were resuspended in PBS and used for flow cytometric determination of inflammatory cells as described below. The same procedure was repeated in each subject after the crossover, with application of the active anti-IgE chamber on the opposite forearm.

Skin testing

Immediately after the start of incubation with anti-IgE in the chambers, anti-IgE (1:100 in PBS, 50 μ l) was injected intradermally on the same forearm midway between the chamber and the elbow. Histamine (3 nmol in 50 μ l PBS) and PBS (50 μ l) were similarly injected on the contralateral arm incubated with control IgG in the chamber. After the crossover, anti-IgE was injected on the opposite arm.

The WFRs (at 10 min) and the subsequent late edema/induration (LPR, 1–6 h) to anti-IgE were delineated on transparent film by one of the investigators. The 10–24-h LPR was similarly recorded by the test subjects themselves after thorough instructions. The areas (cm²) of the skin responses were determined by computer-assisted planimetry.

In separate experiments, the dose of heparin (30 IE/ml PBS) used in the chamber experiments was found not to change significantly the skin responses to intradermal anti-IgE (1:100); i.e., the areas of wheal, flare, and LPR in response to anti-IgE in PBS/heparin were $92.3 \pm 5.8\%$, $104 \pm 13.3\%$, and $122.7 \pm 19.0\%$, respectively, of the corresponding responses to anti-IgE in PBS alone ($n = 4$).

Histamine and α_2 -macroglobulin assays

Histamine was analyzed in duplicate in unpurified skin chamber fluid using a commercially available radioimmunoassay (histamine, radioimmunoassay kit, cat. no. 1302, Immunotech International SA, Marseille, France). In this assay, modified histamine in the sample competes with iodinated histamine tracer for the binding to an antihistamine antibody coated on a test tube (detection limit: 0.05 ng/ml histamine). Standard solution (0–150 nM histamine) or sample was mixed with acylation buffer and incubated in the presence of acylating reagent for 30 min at room temperature. Acylated standard or sample and ¹²⁵I-radiolabeled histamine were then added to the antihistamine antibody-coated tubes. Uncoated tubes with tracer alone were used for determination of total radioactivity. After incubation for 18 h at 2–6°C, the coated tubes were emptied and the bound radioactivity was measured.

The α_2 -macroglobulin content in unpurified skin

chamber fluid was determined by electroimmunoassay according to Laurell (15), using monospecific rabbit antihuman α_2 -macroglobulin immunoglobulin fraction (DAKO A/S, Copenhagen, Denmark). The calibrator was also from DAKO. The assay range for undiluted samples was 9.75–97.5 μ g/ml.

No unspecific histamine or α_2 -macroglobulin immunoreactivity was detected in buffer containing only anti-IgE and/or normal goat IgG.

Analysis of leukocytes

Leukocytes in skin chamber fluid from the 4–8-h sampling period were obtained by centrifugation at 300 g for 5 min (4°C). In order to enable flow cytometric analysis of eosinophils without prior purification procedures, the leukocyte preparations were treated according to the previously described FOG cell membrane permeabilization method (12). Briefly, the permeabilization is obtained by treating paraformaldehyde-fixed leukocytes with *n*-octyl-beta-D-glucopyranoside (OG). This treatment results in scatter-distinguishable eosinophils and permits analysis of both intracellular and surface antigens by flow cytometry.

In some experiments, when a sufficient number of cells could be harvested, the surface expression of CD9 was measured. To obtain optimal binding of monoclonal antibodies to surface antigens and to avoid intracellular binding, antibodies to CD9 (Sera-Lab, Crawley Down, Sussex, UK) were incubated with untreated leukocytes. The surface immunostained cells were then permeabilized by the FOG method to obtain the separated eosinophil population by flow cytometry.

The final leukocyte preparations were analyzed in an EPICS Profile II flow cytometer (Coulter, Inc, Hialeah, FL, USA). The data were collected in list mode and further analyzed by the Elite workstation software (Coulter, Inc), as previously described in detail (12, 13). The eosinophils were identified by their preserved high scatter signals and in some experiments by their surface expression of CD9 (12, 13).

Statistical analysis

Statistical evaluation of potential differences between loratadine and placebo treatment was performed with the Wilcoxon signed ranks test for paired observations. The data were expressed as mean values $\pm$ SE.

Results

All subjects fulfilled the trial, and none of them complained or showed signs of systemic allergic symptoms (e.g., distant skin rash, airway obstruction)

after anti-IgE challenge (applies to both intradermal injections and the skin chamber experiments described below).

Anti-IgE-induced skin inflammation

The cutaneous response to intradermal injection of normal goat IgG (titer 1:100) was indistinguishable from the minor reaction induced by PBS (not shown). Both histamine (3 nmol) and anti-IgE (titer 1:100) caused significant WFRs, while LPRs developed only after anti-IgE injection (Figs. 1 and 2). The LPRs were characterized by distinct, somewhat irregular, erythematous induration and edema, reaching maximum intensity at 6–10 h after challenge.

As compared to placebo treatment, loratadine significantly inhibited the WFRs to anti-IgE by 35% (wheal) and 65% (flare), respectively, and corresponding histamine-induced reactions by 50% and 70%, respectively (Fig. 1). Moreover, loratadine attenuated the initial phase (0–2 h) of the anti-IgE-induced LPR by up to $\approx 60\%$ (Fig. 2). Table 1 shows the individual data for histamine- and anti-IgE-induced WFRs before and after the crossover.

Anti-IgE-induced histamine release in skin chambers

Fig. 3 illustrates anti-IgE-induced (titer 1:10) net release of histamine into skin chamber fluid; i.e., we subtracted the minor histamine release in the contralateral control chambers where the histamine levels were consistently $< 10\%$ of the active anti-IgE sites. In comparison with the placebo period, pretreatment with loratadine had no effect on the IgE-mediated release of histamine.

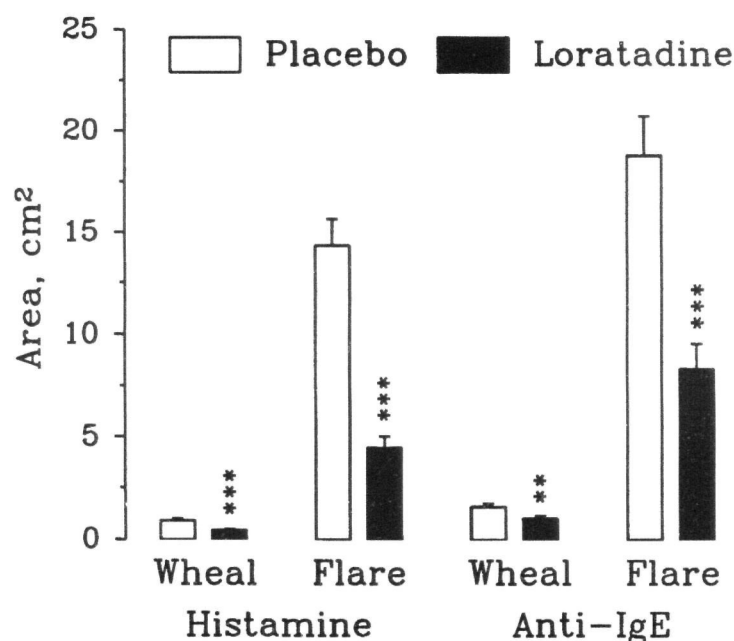


Fig. 1. Size (cm²) of wheal-and-flare reactions 10 min after intradermal injection of antihuman IgE (titer 1:100) or histamine (3 nmol) on volar aspect of forearm of atopic subjects treated with loratadine or placebo. Mean values $\pm$ SE ($n = 10$), ** $P < 0.01$; *** $P < 0.001$.

Loratadine and anti-IgE reactions in skin

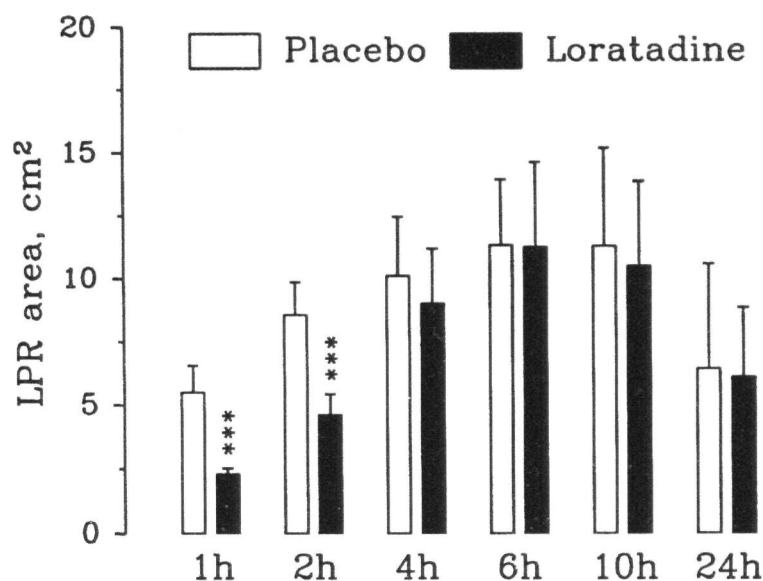


Fig. 2. Size (cm²) of late cutaneous edema/induration (late-phase reaction; LPR) at indicated time points after intradermal injection of anti-IgE (titer 1:100) on volar aspect of forearm of atopic subjects treated with loratadine or placebo. Mean values $\pm$ SE ($n = 10$), *** $P < 0.001$.

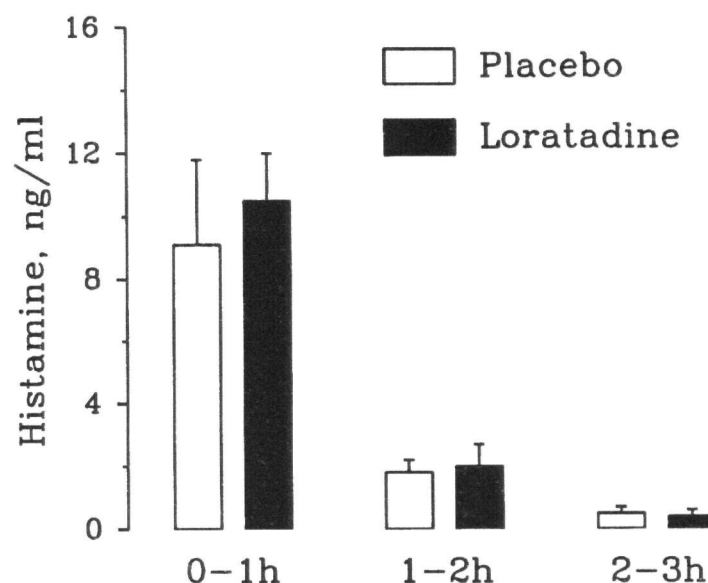


Fig. 3. Net release of histamine into skin chamber fluid at indicated time points after local challenge with anti-IgE (titer 1:10) in atopic subjects treated with loratadine or placebo. Mean values $\pm$ SE ($n = 10$).

Anti-IgE-induced α_2 -macroglobulin extravasation in skin chambers

The “spontaneous” extravasation of α_2 -macroglobulin into control IgG chambers was relatively high; i.e., when considered as total α_2 -macroglobulin accumulation during the 0–8-h observation period as a whole, it was $57.3 \pm 4.6\%$ of the corresponding value for anti-IgE chambers ($n = 10$). In other words, after challenge with anti-IgE, the α_2 -macroglobulin concentrations rose by approximately 100% (Fig. 4), and this increase was statistically significant at all time points in both groups (P values between 0.001 and 0.032). However, there were no statistical differences in evoked α_2 -macroglobulin extravasation between the placebo and loratadine periods ($P > 0.1$ at all time points).

Table 1. Effects of loratadine and placebo on histamine- and anti-IgE-induced wheal-and-flare reactions in skin of atopic subjects

Patient	1	Histamine		algE		2	Histamine		algE	
		Wheal	Flare	Wheal	Flare		Wheal	Flare	Wheal	Flare
SH	P	1.46	9.13	1.22	7.49	L	0.50	1.76	0.56	3.08
ALE	P	0.91	18.25	1.58	25.47	L	0.41	5.15	1.24	10.81
JH	P	1.03	20.13	1.93	20.66	L	0.44	5.13	1.32	13.28
ACC	P	0.85	8.19	1.24	20.30	L	0.46	6.21	1.51	9.71
AB	P	0.98	16.67	1.70	19.58	L	0.16	1.50	0.74	3.32
CS	L	0.29	6.35	1.16	11.21	P	1.07	15.36	1.57	26.89
AC	L	0.58	3.39	0.39	2.38	P	0.97	14.71	2.92	19.48
HE	L	0.68	5.60	1.37	10.50	P	1.03	9.98	1.21	10.26
RB	L	0.63	4.69	1.14	9.96	P	0.67	17.79	1.25	15.77
PJ	L	0.51	5.19	1.15	9.18	P	0.57	13.43	1.43	22.01

Individual data for sizes (cm²) of wheal-and-flare reactions 10 min after intradermal injection of histamine (3 nmol) or antihuman IgE (algE, titer 1:100) on volar aspect of forearm of atopic subjects treated with loratadine (L) or placebo (P). Half of patients received loratadine during first treatment period (1), and other half placebo. Crossover treatment (2) was performed after 7-day washout period.

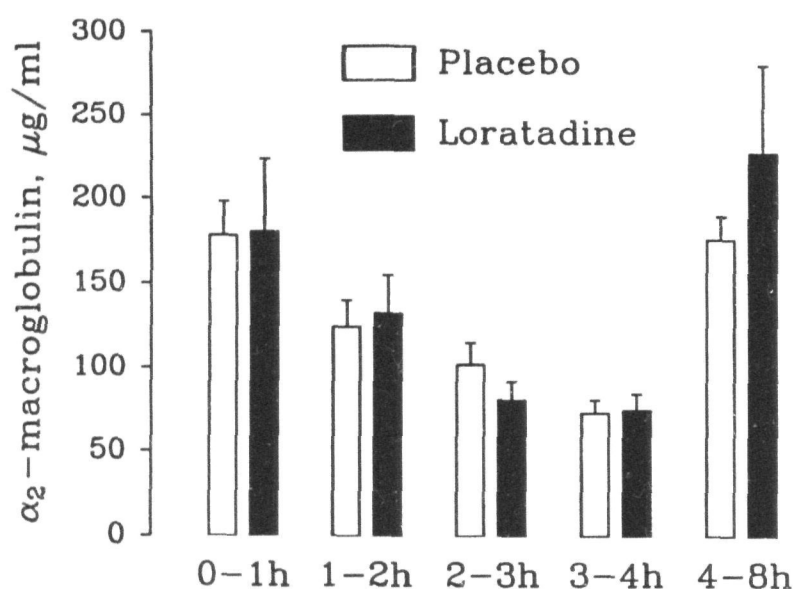


Fig. 4. Net accumulation of α_2 -macroglobulin in skin chamber fluid at indicated time points after local challenge with anti-IgE (titer 1:10) in atopic subjects treated with loratadine or placebo. Mean values $\pm$ SE ($n = 10$).

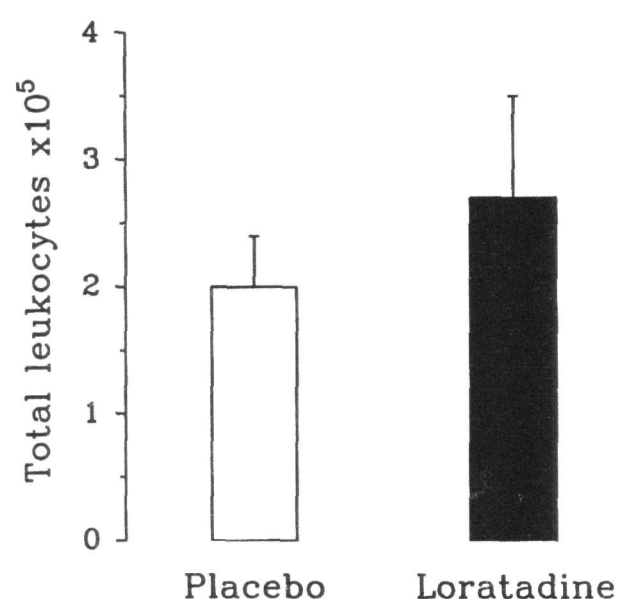


Fig. 5. Net recruitment of all subtypes of leukocytes into skin chamber fluid 4-8 h after local challenge with anti-IgE (titer 1:10) in atopic subjects treated with loratadine or placebo. Mean values $\pm$ SE ($n = 10$).

Anti-IgE-induced leukocyte recruitment in skin chambers

As measured in the 4-8-h samples, the net recruitment of mixed leukocytes into chambers incubated with anti-IgE was 2.7 ± 0.8 and $2.0 \pm 0.4 \times 10^5$ after loratadine and placebo treatment, respectively (Fig. 5). Of these cells, $7.6 \pm 3.4\%$ and $6.7 \pm 1.4\%$, respectively, were identified as eosinophils (Fig. 6). The corresponding values for total leukocytes in control IgG chambers were 0.7 ± 0.5 and $0.5 \pm 0.5 \times 10^5$, respectively (subtracted from the anti-IgE values in Fig. 5). No significant differences between placebo and loratadine treatment were detected.

To confirm the identity of the cells within the defined eosinophil gate, monoclonal antibodies to CD9 were incubated with chamber leukocytes recruited by anti-IgE when a sufficient number of cells could

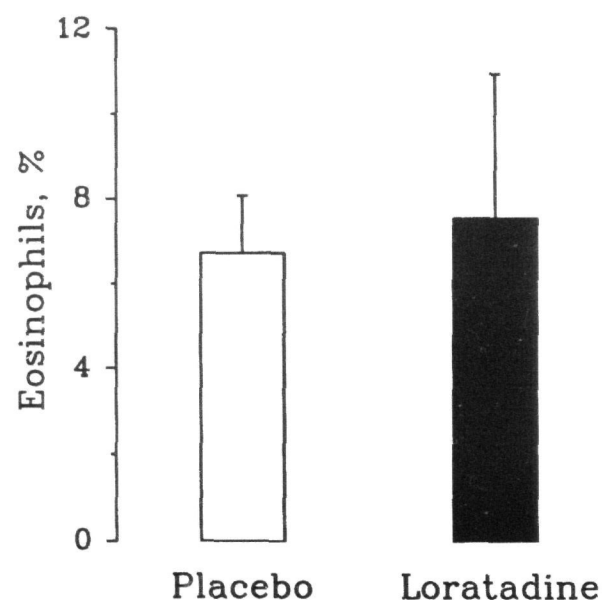


Fig. 6. Eosinophils (in percentage of total leukocytes shown in Fig. 5) in skin chamber fluid at 4-8 h after local challenge with anti-IgE (titer 1:10) in atopic subjects treated with loratadine or placebo. Mean values $\pm$ SE ($n = 10$).

be harvested ($n = 5$). The percentage of CD9-positive cells within the given eosinophil gate was $92 \pm 3.5\%$.

Discussion

We have described the effects of loratadine treatment on anti-IgE-induced inflammation in the skin of atopics. Loratadine was administered in a double therapeutic dose (20 mg/day), and, because steady-state levels of this drug are achieved by day 5 of repeated dosage (9), treatment was begun 1 week prior to the experiments.

In agreement with effects on allergen-induced immediate skin reactions (25), loratadine effectively antagonized WFRs induced by anti-IgE. The subsequent LPR was attenuated by up to 60% during the first 2 h after challenge. In concomitantly performed skin chamber experiments, loratadine did not modify the anti-IgE-induced histamine release. Thus, as shown previously for cetirizine (6) and terfenadine (16), loratadine seems to lack "mast-cell-stabilizing" activity in the skin of atopics. This is in contrast to allergen challenge in the nose, where both loratadine and terfenadine inhibit release of histamine as well as prostaglandin D_2 (1, 3, 20). Interestingly, cetirizine appears to be inactive in this regard (19). We also found that loratadine had no effect on anti-IgE-induced recruitment of eosinophils (or other leukocytes). This is in agreement with previous reports on terfenadine and astemizole (2, 16). In contrast, cetirizine has been found to inhibit antigen-induced influx of eosinophils into skin blister sites in several well-controlled studies (5, 10, 17). Furthermore, both terfenadine and loratadine reportedly attenuate the late influx of inflammatory cells (including eosinophils) into the conjunctiva after allergen challenge in patients with allergic rhinoconjunctivitis (7, 8). Obviously, all these drugs can indeed antagonize mediator release and/or influx of inflammatory cells; however, there seem to be both drug and organ specificities that remain to be mechanistically explained. Moreover, the clinical relevance of the apparently differential effects of the different antihistamines needs further characterization.

α_2 -macroglobulin has previously been shown to be a useful marker for plasma protein extravasation in nasal and bronchial lavage after allergen challenge in atopics (24), and we found that anti-IgE markedly increased the extravasation of α_2 -macroglobulin also in skin chambers. This evoked protein leakage was significantly increased during the whole 8-h sampling period; however, there were no differences between loratadine and placebo treatment in this respect. Knowing that loratadine reduced the edema formation associated with both the immediate wheal reaction and the initial phase of the LPR in intact skin challenged with anti-IgE, we were surprised that

the extravasation of α_2 -macroglobulin into skin chambers was not reduced by loratadine treatment. Yet, this is analogous with data on cetirizine in atopics which showed no effect on protein leakage into skin chambers 30 min after challenge with allergen (18). At present, we cannot explain this apparent discrepancy between intact skin and skin chambers. However, because loratadine has been shown to reduce allergen-induced protein extravasation in the nasal mucosa where the experimental procedure causes no or only minimal tissue trauma (1), it cannot be excluded that the observed "spontaneous" protein leakage associated with the induction of blisters may conceal a partial inhibition of evoked extravasation of plasma proteins.

In summary, loratadine caused clear-cut inhibition of anti-IgE-induced wheal and flare, while only the first part of the subsequent LPR was reduced. On the other hand, loratadine did not affect anti-IgE-induced histamine release or accumulation of leukocytes. Thus, if we assume that the major effect of histamine in skin is H_1 -receptor-mediated acute edema and hyperemia, our results indicate that the antiallergic effects of loratadine in the skin of atopics are related to specific histamine-receptor blockade without interference with other inflammatory effector mechanisms such as mediator release and leukocyte recruitment. Thus, in contrast to, for example, cetirizine, loratadine may be a useful tool in skin experiments when selective antagonism of histamine-receptors is desired.

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