with loratadine, 10 mg once daily, terfenadine, 60 mg twice daily, or placebo on the early response to nasal challenge with allergen, the subsequent cellular influx, and the increased responsiveness to methacholine 24 h later (23). Both loratadine and terfenadine treatment resulted in significant reductions in allergen-induced sneezing and in the levels of histamine, kinins, albumin, and TAME-esterase activity in recovered nasal lavage, with no significant differences between the treatments (Fig. 5). Neither treatment decreased the levels of tryptase, PGD₂, or LTC₄. There was a significant increase in total eosinophils 24 h after allergen challenge in the placebo group, and this was not affected by loratadine or terfenadine treatment. A significant increase in reactivity to methacholine, as assessed by weights of secretions, was found 24 h after allergen challenge compared to screening challenge, and both antihistamines prevented this. These results suggest that loratadine may not only antagonize the effects of histamine following its release from mast cells after the early response to nasal challenge with allergen, but also inhibit subsequent cellular influx and allergen-induced hyperresponsiveness of the nasal mucosa.

Raptopoulou-Gigi and colleagues treated patients with allergic rhinitis with either loratadine, 10 mg daily, or placebo for 1 month during a high-pollen-count period (102). Loratadine-treated patients had significantly lower symptom scores and, at the end of treatment, the numbers of cells expressing IL-2R, HLA-DR, and proliferating cell nuclear antigen (PCNA) in the nasal biopsies were significantly decreased in the loratadine-treated group. How loratadine exerted its inhibitory effect on the activation of T cells is unknown. Furthermore, Greiff and colleagues (103) have investigated the effect of treatment with loratadine 20 mg daily for 5 days on allergen-induced changes in the level of tryptase and α2-macroglobulin in 12 subjects with allergic rhinitis in a randomized, double-blind, placebo-controlled, crossover trial. Loratadine significantly decreased nasal symptoms as well as the release of tryptase and α2-macroglobulin during the EPR, but did not affect the number of eosinophils during the LPR. The reduction in both mediators suggests that loratadine inhibits mast cell activation and modulates the permeability of the microvasculature in the nasal mucosa.

Ciprandi and colleagues (67) conducted a randomized, double-blind, parallel study in 20 seasonal allergic rhinitis subjects examining the effect of 2 weeks treatment with loratadine 10 mg daily and cetrizine 10 mg daily on cellular infiltration and expression of adhesion molecules after natural allergen exposure. Loratadine and cetrizine significantly reduced symptoms, eosinophil and metachromatic cell infiltration, levels of ECP and histamine in nasal lavage fluid, and ICAM-1 expression on nasal epithelial cells compared to the pretreatment baseline (Table 3). The reduction of ICAM-1 expression on the conjunctival epithelium by loratadine was also shown in a study of allergen-specific conjunctival challenge (104). Loratadine and its metabolite desloratadine decrease histamine-induced expression of ICAM-1 on nasal epithelial cells in vitro significantly
Figure 5  Effects of loratadine and terfenadine on nasal challenge with allergen. In a double-blind, placebo-controlled, three-way crossover study, 14 asymptomatic allergic individuals were treated with loratadine 10 mg daily, terfenadine 60 mg twice daily, or placebo for 1 week. Nasal challenge and lavage were then performed. Twenty-four hours later, the lavage was repeated, and methacholine challenge was performed to assess allergen-induced increased nasal hyperreactivity. Mediator levels were measured in nasal lavage fluid. The net changes from the diluent challenge for each parameter are shown as mean ± SEM. Compared with placebo, both loratadine and terfenadine significantly decreased allergen-induced sneezing and the levels of histamine, kinins, TAME-esterase activity, and albumin in recovered nasal lavage, with no significant differences between the two treatments. *p < 0.05 vs. placebo; TAME, N-α-tosyl L-arginine methyl ester. (From Ref. 23.)
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Loratadine</th>
<th>Cetirizine</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>p value</td>
</tr>
<tr>
<td>Clinical score</td>
<td>13 (11–16)</td>
<td>2 (0–7)</td>
<td>0.002</td>
</tr>
<tr>
<td>ICAM-1 positivity</td>
<td>2 (1–3)</td>
<td>0 (0–1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>4 (2–5)</td>
<td>3 (1–4)</td>
<td>NS</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>3 (2–6)</td>
<td>2.5 (1–5)</td>
<td>0.016</td>
</tr>
<tr>
<td>Metachromatic cells</td>
<td>2 (1–4)</td>
<td>1 (1–2)</td>
<td>0.01</td>
</tr>
<tr>
<td>ECP (µg/L)</td>
<td>38.5 (30–51)</td>
<td>26 (15–31)</td>
<td>0.002</td>
</tr>
<tr>
<td>EPO (µg/L)</td>
<td>50 (29–63)</td>
<td>41 (19–58)</td>
<td>0.006</td>
</tr>
<tr>
<td>MPO (µg/L)</td>
<td>81 (50–133)</td>
<td>96 (52–238)</td>
<td>NS</td>
</tr>
<tr>
<td>Histamine (µg/L)</td>
<td>0.2 (0.1–3.7)</td>
<td>0.1 (0.0–0.7)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

In a randomized, double-blind, parallel design, 20 subjects with allergic rhinoconjunctivitis were treated with either loratadine 10 mg daily or cetirizine 10 mg daily for 2 weeks during natural allergen exposure. The parameters were compared before and after treatment. The data are presented as median (range). Cells and mediators were measured in nasal lavage fluid. ICAM-1, intercellular adhesion molecule-1; ECP, eosinophil cationic protein; EPO, eosinophil peroxidase; MPO, myeloperoxidase; NS, not significant.

Source: Ref. 67.
These studies demonstrate that loratadine provides an antiallergic effect by modulating ICAM-1 expression on epithelial cells. The different results, compared with earlier studies, could be related to differences in the design, techniques, and outcome measures used.

Miadonna and colleagues studied 10 subjects with allergic rhinitis due to dust mites, who were treated with loratadine (10 mg daily) and with placebo for 1 week, in a double-blind, crossover trial (106). Subjects treated with placebo had nasal symptoms after allergen challenge, followed by a significant increase in histamine concentration in nasal lavage fluid collected 5 min after stimulation. Loratadine significantly reduced allergen-induced nasal symptoms and histamine release in the 5 min, 10 min, and 20 min postchallenge lavages (Table 4). The results of this study are consistent with those of earlier studies (23, 97, 98). Furthermore, ex vivo basophil histamine release induced by anti-IgE (10 μg/mL), formyl methionyl leucyl phenylalanine (fMLP) (1 μM), and Ca\textsuperscript{2+} ionophore A23187 (1 μM) was reduced significantly after treatment with loratadine. The most interesting feature is that loratadine also inhibited histamine release from basophils activated by different agents. Although anti-IgE, fMLP, and Ca\textsuperscript{2+} ionophore A23187 have different mechanisms of action, they all cause an increase in intracellular Ca\textsuperscript{2+} concentration. A previous study has shown that one possible mecha-

| Table 4 | Effect of Loratadine on Histamine Levels in Early Allergic Inflammation |
|---------|-----------------------------|-----------------------------|-----------------------------|
| Nasal lavage | Placebo | Loratadine | p value |
| Prechallenge | | | |
| 1st | 6.5 (2–25) | 6.5 (2–40) | NS |
| 5th | 0.5 (0–1) | 0.5 (0–2) | NS |
| Postchallenge | | | |
| 5 min | 4 (1–28) | 0.5 (0–3) | <0.01 |
| 10 min | 0.5 (0–5) | 0 (0–1) | <0.001 |
| 20 min | 0 (0–2) | 0 (0–0) | <0.01 |
| 30 min | 0 (0–1) | 0 (0–0) | NS |
| 60 min | 0 (0–0) | 0 (0–0) | NS |

Ten asymptomatic subjects with allergic rhinitis were treated with loratadine 10 mg daily and with placebo for 1 week before allergen challenge. Nasal lavages were done before and after challenge with the relevant allergen after each treatment period. Five nasal lavages were performed at 4-min intervals before allergen challenge in order to obtain low and uniform prechallenge histamine levels (1st: first prechallenge lavage; 5th: fifth prechallenge lavage). Nasal lavages were repeated 5, 10, 20, 30, and 60 min after allergen challenge. Results are histamine levels in nasal lavage fluids (ng/mL) before and after allergen challenge. The data are median (range) for 10 subjects. NS, not significant. 

Source: Ref. 106.
nism by which an antiallergic drug can inhibit histamine release is through induction of membrane stabilization (107). It is reasonable to speculate that the inhibitory effect of loratadine on basophil histamine release is related to its effect on membrane stabilization, transmembrane Ca\(^{2+}\) influx, and intracellular Ca\(^{2+}\) increase.

K. Mizolastine

Mizolastine, a novel benzimidazole derivative, is highly selective for histamine H\(_1\)-receptors and has no anticholinergic, antiadrenergic, or antiserotoninergic activity. At a dosage of 10 mg daily it reduces the symptoms associated with seasonal and perennial allergic rhinitis (108, 109). Anti-inflammatory properties of mizolastine were demonstrated in animal experiments (110, 111). Levrier and colleagues studied the antiallergic activities of mizolastine in actively sensitized guinea pigs and passively sensitized rats (110). Mizolastine significantly reduced allergen-induced release of histamine from mast cells in bronchoalveolar lavage fluid of guinea pigs and in the peritoneal fluid of sensitized rats. This study suggests a potential mast cell inhibitory role for this agent in allergen-induced reactions.

Pichat and colleagues studied the effects of mizolastine, loratadine, terfenadine, and pyrilamine on arachidonic acid (AA)-induced edema in the rat paw (111). Mizolastine significantly inhibited AA-induced paw inflammation in a dose-dependent manner, whereas other antihistamines failed to inhibit the inflammatory action of AA. These data suggest inhibitory effects of mizolastine on AA-induced inflammation. Mizolastine is one of the newest antihistamines and there are few published data on its antiallergic effects in humans.

L. Oxatomide

Oxatomide is an H\(_1\)-receptor antagonist chemically related to cinnarizine, with potent antihistaminic activity and inhibitor effects on mast cell degranulation (112). In addition, oxatomide exerts some antiserotonin, anticholinergic activity, and anti-slow-reacting substance of anaphylaxis (SRSA) in in vitro and in vivo models (113). Preincubation of basophils with oxatomide (10\(^{-7}\)–10\(^{-5}\) mol/L) concentration dependently inhibited the immunological release of histamine and LTC\(_4\) before anti-IgE challenge (114). Oxatomide (10\(^{-7}\)–10\(^{-5}\) mol/L) also reduced histamine, tryptase, and LTC\(_4\) release from human lung mast cells (HLMC) activated by anti-IgE.

The efficacy of oxatomide (30 mg daily) in the treatment of seasonal allergic rhinitis and/or conjunctivitis has been demonstrated in a double-blind, placebo-controlled study (115).

To study the effect of 4 weeks of treatment with azelastine (orally 1 mg twice a day) and oxatomide (orally 30 mg twice a day) on substance P (SP)
Table 5  In Vivo Studies of the Effect of H1-Antihistamines on Nasal Allergic Inflammation Either After Nasal Challenge with Allergen or During Natural Allergen Exposure

<table>
<thead>
<tr>
<th>Drug</th>
<th>Early phase</th>
<th>Late phase</th>
<th>Hyperresponsiveness in vivo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Azatadine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Togias et al. (39) NCA</td>
<td>↓ Histamine, TAME-esterase, kinin</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td><strong>Azelastine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Intranasal)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelucchi et al. (57) NAE</td>
<td>No effect: eosinophils</td>
<td>↓ ECP in nasal lavage, neutrophils, eosinophils, ICAM-1 expression on nasal epithelial cells</td>
<td>NE</td>
</tr>
<tr>
<td>Ciprandi et al. (54) NCA</td>
<td>↓ Neutrophils, eosinophils, ICAM-1 expression on nasal epithelial cells</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td><strong>Cetirizine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naclerio et al. (60) NCA</td>
<td>↓ TAME-esterase, LTC₄, albumin</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Klementsson et al. (65) NCA</td>
<td>NE</td>
<td>No effect: eosinophils</td>
<td>↓ increased nonspecific hyperreactivity to methacholine</td>
</tr>
<tr>
<td>Ciprandi et al. (68) NAE</td>
<td>↓ ICAM-1 expression on nasal epithelial cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprandi et al. (66) NAE</td>
<td>↓ Neutrophils, eosinophils, ICAM-1 expression on nasal epithelial cells, sICAM-1, ECP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Effect</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>------------------------------</td>
<td>---------------------------------------------</td>
<td>------------------------------</td>
<td></td>
</tr>
<tr>
<td>Campbell et al. (73) NAE</td>
<td>↓ sICAM-1</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Ciprandi et al. (67) NAE</td>
<td>↓ Eosinophils, neutrophils, metachromatic cells, ICAM-1 expression on nasal epithelial cells, ECP, EPO, histamine</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Jacobi et al. (59) NCA</td>
<td>↓ Histamine, tryptase</td>
<td>NE</td>
<td></td>
</tr>
<tr>
<td><strong>Ebastine</strong></td>
<td></td>
<td>NE</td>
<td></td>
</tr>
<tr>
<td>Campbell et al. 1996 (78) NCA</td>
<td>No effect: LTC_4, LTD_4, PGD_2, GM-CSF, TNF-α, IL-8</td>
<td>↓ GM-CSF - No effect: LTC_4, LTD_4, PGD_2, TNF-α, IL-8</td>
<td></td>
</tr>
<tr>
<td><strong>Ketotifen</strong></td>
<td></td>
<td>NE</td>
<td></td>
</tr>
<tr>
<td>Majchel et al. (87) NCA</td>
<td>No effect: TAME-esterase, histamine</td>
<td>NE</td>
<td></td>
</tr>
<tr>
<td>Kato et al. (88) NAE</td>
<td>↓ Blood eosinophil count, serum ECP</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Kato et al. (89) NAE</td>
<td>↓ Blood eosinophil count, serum MBP</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td><strong>Levocabastine</strong></td>
<td></td>
<td>NE</td>
<td></td>
</tr>
<tr>
<td>(Intranasal)</td>
<td></td>
<td>NE</td>
<td></td>
</tr>
<tr>
<td>Padgrak et al. (95) NCA</td>
<td>NE</td>
<td>↓ albumin, neutrophils, eosinophils, metachromatic cells</td>
<td></td>
</tr>
<tr>
<td><strong>Bachert et al. (94) NCA</strong></td>
<td>No effect: albumin</td>
<td>NE</td>
<td></td>
</tr>
<tr>
<td>de Graaf et al. (92) NCA</td>
<td>No effect: albumin, tryptase</td>
<td>NE</td>
<td></td>
</tr>
<tr>
<td>Svensson et al. (93) NCA</td>
<td>No effect: albumin</td>
<td>NE</td>
<td></td>
</tr>
<tr>
<td><strong>Loratadine</strong></td>
<td></td>
<td>NE</td>
<td></td>
</tr>
<tr>
<td>Bousquet et al. (97) NCA</td>
<td>↓ Histamine, PGD_2</td>
<td>NE</td>
<td></td>
</tr>
<tr>
<td>Andersson et al. (98) NCA</td>
<td>↓ Histamine, TAME-esterase</td>
<td>NE</td>
<td></td>
</tr>
<tr>
<td>Naclerio et al. (101) NCA</td>
<td>No effect: histamine, PGD_2, LTC_4, albumin, kinin</td>
<td>NE</td>
<td></td>
</tr>
<tr>
<td>Raptopoulou et al. (102) NAE</td>
<td>↓ IL-2R, HLA-DR, PCNA positive cells</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Early phase</td>
<td>Late phase</td>
<td>Hyperresponsiveness in vivo</td>
</tr>
<tr>
<td>------------------------------</td>
<td>--------------------------------------</td>
<td>---------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Greiff et al. (103) NCA</td>
<td>↓ Tryptase, α2-macroglobulin</td>
<td>No effect: eosinophils</td>
<td>NE</td>
</tr>
<tr>
<td></td>
<td>↓ Histamine, kinin, albumin,</td>
<td>No effect: eosinophils</td>
<td>↓ increased nonspecific hyperreactivity to methacholine</td>
</tr>
<tr>
<td></td>
<td>TAME-esterase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baroody et al. (23) NCA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprandi et al. (67) NAE</td>
<td>No effect: tryptase, PGD₂, LTC₄</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>↓ Eosinophils, metachromatic cells,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ICAM-1 expression on nasal epithelial</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>cells, ECP, EPO, histamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Campbell et al. (73) NAE</td>
<td>↓ sICAM-1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Miadonna et al. (106) NCA</td>
<td>↓ Histamine</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Oxatomide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shinoda et al. (121) NAE</td>
<td>↓ SP</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

NCA, nasal challenge with allergen; NAE, natural allergen exposure; NE, not evaluated; IL, interleukin; LT, leukotriene; TAME, N-alpha-tosyl-L-arginine methyl ester; GM-CSF, granulocyte macrophage colony-stimulating factor; ECP, eosinophil cationic protein; ICAM-1, intercellular adhesion molecule-1; SP, substance P; sICAM-1, soluble intercellular adhesion molecule-1; EPO, eosinophil peroxidase; TNF, tumor necrosis factor; PG, prostaglandin; MBP, major basic protein; HLA-DR, human leukocyte antigen-DR.
and vasoactive intestinal peptide (VIP) levels in nasal secretions, Shinoda and colleagues performed a randomized, double-blind, parallel study in 40 subjects with house dust allergy and 210 healthy subjects (116). Mean values of SP, but not VIP, were significantly higher in the nasal allergy group than in the control group. Patients with severe symptoms had significantly higher levels of SP and VIP in nasal secretions than those in the control group. Oxatomide and azelastine significantly reduced SP levels in nasal secretions, and VIP levels were suppressed by 70%, although this did not achieve statistical significance.

The mechanism by which oxatomide decreases neuropeptides in nasal secretions is unknown. Eosinophils from human peripheral blood were demonstrated to contain significantly higher levels of SP and VIP than did neutrophils, mononuclear leukocytes, and platelets (117). One possible mechanism for the decrease of the neuropeptides in nasal secretions after oxatomide administration might be the reduction of eosinophil infiltration into nasal secretions. This hypothesis is supported by the study of Ciprandi and colleagues (118). Using allergen-specific conjunctival challenge, they demonstrated that oxatomide significantly decreased total numbers of inflammatory cells as well as the number of single cell types (neutrophils, eosinophils, and lymphocytes) during the early- and late-phase reactions.

M. Terfenadine

From an historical point of view, terfenadine was one of the first H₁-antagonists to be investigated for antiallergic properties, and was one of the most comprehensively studied. Rarely, it caused cardiac toxicity, and regulatory approval was withdrawn for it in most countries. In addition to its H₁-receptor antagonist effects it also inhibits the anti-IgE-induced release of histamine, LTC₄, and PGD₂ from human lung mast cells in vitro (119). After allergen challenge in subjects with allergic rhinitis, pretreated with terfenadine, the following have been reported: reduced symptoms, decreased histamine, kinins, albumin and TAME-esterase activity, decreased inflammatory cell infiltrates and ICAM-1 expression on nasal epithelial cells, and ECP in lavage fluid (120–125).

V. SUMMARY

Data from in vitro, in vivo, and ex vivo studies suggest that second-generation antihistamines have a number of antiallergic, anti-inflammatory properties that appear to be independent of their H₁-blockade activity. First-generation antihistamines also have antiallergic, anti-inflammatory properties, as suggested by the studies with azatadine, chlorpheniramine, mepyramine, and promethazine; most other first-generation antihistamines have not been studied for these properties.
In vitro studies have shown that H<sub>1</sub>-antihistamines reduce the release of pro-inflammatory mediators from mast cells and basophils, the chemotaxis and activation of inflammatory cells (especially eosinophils), and the expression of adhesion molecules induced by immunological and nonimmunological stimuli in epithelial cell lines. Nasal allergen challenge models have similarly demonstrated that H<sub>1</sub>-antihistamines inhibit mediator release from mast cells and basophils, and that they decrease inflammatory cell infiltration and the expression of adhesion molecules on epithelial cells. The results of published studies of the effects of H<sub>1</sub>-antihistamines on nasal allergic inflammation in humans have been summarized in this chapter. Recent investigations indicate that H<sub>1</sub>-antihistamines may modulate airway inflammation by downregulating the activity of airway epithelial cells, which have an important role in allergic airway inflammation. The modulation of adhesion molecules and of inflammatory cell infiltration by H<sub>1</sub>-antihistamines may be beneficial during long-term treatment in patients with allergic rhinitis. The rationale for this hypothesis is the persistence of inflammation on the nasal epithelial cells even when patients are symptom-free (16). All of the events affected by H<sub>1</sub>-antihistamines are important in the allergic inflammation cascade. The underlying mechanisms for such effects remain unclear, but are unrelated to H<sub>1</sub>-antagonist activity. Several studies have demonstrated that H<sub>1</sub>-antihistamines can form an ionic association with cell membranes and inhibit calcium ion influx into the mast cell or basophil plasma membrane, or inhibit Ca<sup>2+</sup> release within the cells, and may therefore influence the signal transduction pathways. However, these effects appear to occur at concentrations higher than those achieved in therapeutic practice (126–128). It has recently been hypothesized that the anti-inflammatory activity of H<sub>1</sub>-antihistamines may be a consequence of their ability to influence the activation of genes responsible for the expression and synthesis of proinflammatory mediators (129).

The contribution of the antiallergic effects of H<sub>1</sub>-receptor antagonists to their clinical efficacy is not fully understood. There have been no data suggesting that H<sub>1</sub>-antihistamines with well-documented antiallergic properties are superior to the others for which such properties have not been as extensively investigated. Additional studies are needed to elucidate the mechanisms(s) by which H<sub>1</sub>-antihistamines exert anti-inflammatory effects. This knowledge might lead to the development of novel therapies with more potent and specific anti-inflammatory effects.

**ACKNOWLEDGMENTS**

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