

Short communication

Reduction of soluble ICAM-1 levels in nasal secretion by H₁-blockers in seasonal allergic rhinitis

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ICAM-1, a transmembrane glycoprotein promoting adhesion in immunologic and inflammatory reactions, was found to be increased on nasal epithelial cells of patients with allergic rhinitis. Loratadine, an H₁-blocker, was found to reduce *in vitro* the expression of ICAM-1 on nasal epithelial cells. A double-blind, parallel-group study was carried out during the pollen season to compare the effect of two H₁-blockers, cetirizine (10 mg OD) and loratadine (10 mg OD), on the release of soluble ICAM-1 in nasal secretions. A group of untreated patients was used as a control group. sICAM-1 was measured by enzyme immunoassay before and after 2 weeks of treatment. Symptoms were significantly decreased in the actively treated groups. sICAM-1 levels were unchanged in the control group but were significantly reduced in the two treated groups ($P < 0.015$, Wilcoxon's W test). This study shows that two H₁-blockers, loratadine and cetirizine, have a similar effect on sICAM-1 released in nasal secretions during the pollen season.

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H₁-blockers represent the first-line treatment of allergic rhinitis. New generation H₁-blockers, including astemizole, cetirizine, ebastine, loratadine, and terfenadine, block histamine at its H₁-receptor level, and some have been found to have additive antiallergic properties (1). In particular, loratadine blocks the release of mediators after *in vitro* or *in vivo* allergen challenge (for review, see Ref. 2), whereas cetirizine blocks the influx of eosinophils in the skin (3), but not in the nose (4).

Some but not all H₁-blockers can reduce the expression of intercellular adhesion molecule-1 (ICAM-1) on epithelial cell membranes, as shown by *in vitro* studies (5, 6) and *in vivo* studies (7, 8). This effect may be important since this molecule is upregulated on airways epithelial cells in allergic rhinitis (5, 9). Membrane surface ICAM-1 can be studied on cells, but it has been recently observed that there is a correlation between cell membrane expression of ICAM-1 and sICAM-1 in models of keratinocytes (10) and fibroblasts (11).

A double-blind, parallel-group study was carried out during the pollen season to compare the effect

of two H₁-blockers, cetirizine (10 mg OD) and loratadine (10 mg OD), on the release of soluble ICAM-1 in nasal secretions. A group of untreated patients was used as a control group.

Material and methods

Patients

Twenty-three patients ranging in age from 21 to 35 years (median age and 25–75th percentiles: 26, 23–27 years) were enrolled in the study after informed consent and approval of the protocol by the local ethics committee had been obtained. All patients fulfilled the following criteria:

- 1) Patients had presented symptoms of seasonal allergic rhinitis for at least the past 2 years.
- 2) Skin prick tests were positive with a standardized orchard grass pollen extract (Stallergènes Laboratories, Fresnes, France). All patients had elevated titers of serum orchard grass pollen IgE (Phadebas CAP System[®], Pharmacia Diagnostics, Uppsala, Sweden).

3) Patients did not receive specific immunotherapy during the current year, and had not been treated with antihistamines, corticosteroids, or ketotifen during the past 2 weeks. None of the patients had received astemizole for the past 2 months.

Before inclusion in the study, patients were carefully evaluated for the presence of nasal symptoms (nasal discharge, stuffiness, sneezing, and itching). According to severity, each symptom was scored 0 to 3 as in a previous study (12), and only patients with moderate to severe rhinitis were enrolled in the study.

Patients were randomly included in the study. Sixteen patients were assigned to one of the two treatment groups (cetirizine or loratadine), and seven others were not treated but were used as a control group. A double-dummy technique was used, and patients were randomized for inclusion in the treatment (cetirizine or loratadine) or untreated (double-dummy-treated) groups.

Soluble ICAM-1 and albumin measurement

At baseline and after 2 weeks of treatment, the patients underwent nasal lavage of both nostrils, 5 ml of isotonic saline being used in each nostril. The recovery of fluid from nostrils ranged from 3.7 to 5.2 ml. The fluid was recovered on ice and immediately centrifuged. The supernatants were stored at -20°C before measurement of ICAM-1. A commercial sandwich enzyme immunoassay (EIA) (sICAM-1-EASIA Medgenix Diagnostics SA, Fleurus, Belgium) was used to measure sICAM-1. Values were expressed as ng sICAM/ml of nasal fluid. The intra- and interassay coefficient of variation was less than 5% for samples. For the same patient, the experimental samples were assayed in the same run. Levels of albumin were measured by EIA (13).

Evaluation of efficacy of the treatment

Patients were observed for up to 2 weeks. During the trial, patients filled in daily a diary card for nasal (nasal discharge, stuffiness, nasal itching, and sneezing) and ocular (itchy eyes and watery eyes)

symptoms. The severity of symptoms was scored from 0 to 3 (12). Concomitant use of any other antiallergic medication was not permitted.

Pollen counts

Pollen counts were analyzed by the technique of Cour (14).

Study design

The trial was a double-blind, parallel-group study, patients receiving loratadine (10 mg OD), cetirizine (10 mg OD), or placebo in the morning. The compliance with treatment was assessed by counting the number of capsules at the end of the trial. Before and at the end of the treatment, the patients underwent nasal lavage and measurement of sICAM-1.

Fisher's exact test was used to analyze demographic characteristics. Nonparametric tests were used for all efficacy parameters. Wilcoxon's W test was used for within-group data and the Mann-Whitney U test for between-group data. Bonferroni's correction was used. Results are expressed in medians and 25–75th percentiles.

Results

Demographic characteristics of the patients

The characteristics of the patients were similar in age, sex, severity, and duration of rhinitis for the three groups.

Clinical efficacy and safety of the treatment

At entry, patients had similar and nonsignificant median nasal symptom scores in the three groups (Mann-Whitney U test). After 2 weeks, control patients had a nonsignificant reduction in the median symptom score, whereas patients treated with cetirizine or loratadine had a significant reduction in median symptom scores ($P < 0.05$, Wilcoxon's W test). There was no difference in median symptom scores between loratadine- and cetirizine-treated patients (Mann-Whitney U test) (Table 1).

Table 1. Evaluation of efficacy of treatments

	Control group	Loratadine	Cetirizine	P C/L**	P C/Cet**
Day 0	8 (8–10.5)	9 (7.5–10.5)	10.5 (8.5–12)	NS	NS
Days 7–14*	9 (7.3–10.5)	4.6 (3.5–5.8)	4.4 (3.5–5.7)	<0.005	<0.005
P value***	NS	<0.015	<0.015		

* Median score. C: control group, L: loratadine, Cet: cetirizine. **P value by Mann-Whitney U test. ***P value by Wilcoxon's W test.

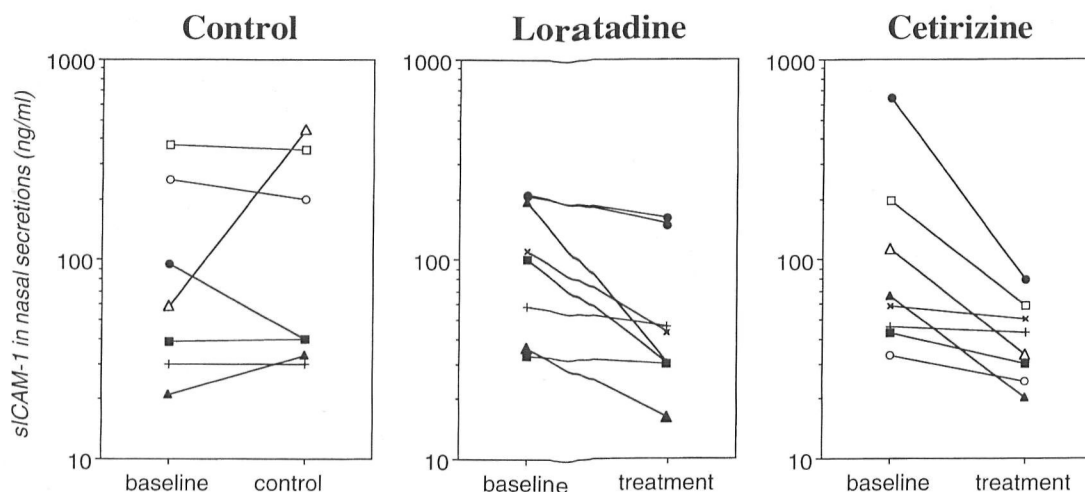


Fig. 1. Soluble ICAM-1 levels recovered in nasal secretions during seasonal allergic rhinitis before and after 2 weeks of intervention.

Pollen counts

Pollen counts were high throughout the study, ranging from 10 to 75/m³ air.

Evolution of sICAM-1 and albumin levels in nasal secretions

Soluble ICAM-1 levels in nasal secretions were similar in the three groups of patients before treatment (Fig. 1). Their median levels did not change in the control group, whereas there was a significant ($P < 0.015$, Wilcoxon's W test) reduction in both treated groups. Median albumin levels in nasal secretions were similar in the three groups and did not change significantly during treatment (data not shown).

Discussion

This study shows that two H₁-blockers, loratadine and cetirizine, have a similar downregulating effect on sICAM-1 released in nasal secretions during the pollen season.

ICAM-1 is a transmembrane glycoprotein which promotes adhesion in inflammatory reactions (15). ICAM-1 is constitutively expressed on cells of many lineages, and *in vitro* studies have shown that cell-surface ICAM-1 and sICAM are upregulated by inflammatory cytokines, including TNF- α , IL-1, IL-6, and IFN- γ (16), and proinflammatory mediators such as histamine (17). An increased membrane expression of ICAM-1 has been found on nasal and bronchial epithelial cells of patients suffering from allergic rhinitis (5, 9) and asthma (18). A significant increase in cell-surface and released sICAM-1 in the epithelial cell line WI 26 is stimulated by IFN- γ , suggesting that the meas-

urement of sICAM-1 in secretions (paper in preparation) reflects the expression of the molecule at the cell-surface level.

The results of the present study indicate that two H₁-blockers, loratadine and cetirizine, can block the release of sICAM-1 in nasal secretions during the pollen season and confirm previous studies on the effects of cetirizine and terfenadine on epithelial cell membrane ICAM-1 (7, 8). Moreover, this study extends *in vitro* studies on loratadine, which has been shown to reduce the expression of ICAM-1 on epithelial cells, stimulated by histamine (6). This is the first demonstration that loratadine can reduce ICAM-1 levels *in vivo*. However, it is not known whether sICAM-1 measured in nasal secretions is due to its release or shedding by activated epithelial cells, since several cells may release this adhesion molecule.

The exact significance of the results is not fully understood since soluble forms of ICAM-1 have been reported to inhibit LFA-1/ICAM-1-mediated adhesion *in vitro*, and it is conceivable that soluble ICAM-1 may regulate LFA-1/ICAM-1-mediated cell-cell interaction (19). sICAM-1 significantly inhibits adhesion of lymphocytes and monocytes to cytokine-stimulated endothelial cells (20).

It is likely that ICAM-1 is an important adhesion molecule which is involved in the nasal inflammatory response (5, 21), and the effects of some H₁-blockers may be of relevance, but the exact *in vivo* importance of these effects must be clarified by further studies.

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