

Short communication

Onset of action in the nasal antihistaminic effect of cetirizine and loratadine in patients with allergic rhinitis

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Several studies have compared the cutaneous efficacy of cetirizine and loratadine and their onset of action. We assessed the nasal effect of these two antihistamines in a randomized, double-blind, crossover, placebo-controlled trial in order to compare objectively their efficacy and onset of action in the noses of patients with allergic rhinitis. Nasal challenge was performed by nebulization of increasing doubling doses of histamine (0, 0.04–1.28 mg/nostril) in 12 patients (eight men, four women, aged 22–39 years). Nasal airway resistance (NAR) was measured by posterior rhinomanometry either 1.5 h or 4 h after intake of cetirizine (10 mg), loratadine (10 mg), or placebo. Baseline NAR was identical between all study days ($2.60\text{--}2.88\text{ cmH}_2\text{O}\cdot\text{l}^{-1}\cdot\text{s}$). One and a half hours after intake, the increase in NAR induced by histamine was significantly reduced by both cetirizine and loratadine in contrast to placebo. However, with cetirizine the nasal obstruction was significantly lower than with loratadine ($P < 0.05$). Four hours after intake, a similar inhibition of the nasal obstruction caused by histamine was observed with both cetirizine and loratadine ($P < 0.05$). In conclusion, this study found cetirizine and loratadine to have similar nasal efficacy at therapeutic dosage 4 h after intake, whereas cetirizine was more effective than loratadine 1.5 h after intake. In agreement with the results observed in the skin, our study suggests a more rapid onset of action of cetirizine in the nose in allergic rhinitis.

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In allergic rhinitis, histamine released by mast cells participates in the early nasal response to antigen. Both in patients with allergic rhinitis and in healthy volunteers, exogenous histamine applied locally to the nasal mucosa partially mimics the nasal response to antigen (1, 2); i.e., it induces vasodilation and edema of the nasal mucosa, leading to nasal obstruction. In man, H_1 -receptor antagonists reduce the nasal obstruction caused by histamine (2), as well as by natural and experimental exposure to allergen (3–5).

Cetirizine and loratadine are two second-generation antihistamines widely used to treat allergic rhinitis and urticaria (6–13). Peak plasma

concentration occurs about 1 h after intake for both antihistamines (14, 15). In the skin, significant antihistaminic effect is observed for cetirizine from 0.5 h after intake (16) and for loratadine from 1 h after intake of 10 mg (17, 18).

We designed a double-blind, randomized, crossover, placebo-controlled study to compare the early nasal inhibitory effect of cetirizine and loratadine, 1.5 h after intake, in patients with allergic rhinitis. A study of the maximal antihistaminic effect was performed 4 h after intake. However, since tachyphylaxis to histamine may occur in the airways, this control was performed 4–7 days later. Nasal airway resistance (NAR) was measured by

posterior rhinomanometry after administration of increasing doubling doses of histamine, as previously described (2).

Material and methods

Patients

Twelve patients (eight men and four women, mean age $\pm$ SD: 27 ± 5 years) with allergic rhinitis participated in the study. They were free of nasal symptoms and of treatment for at least 1 month before inclusion and before each histamine provocation challenge test. All gave their informed written consent to participate. The study was approved by the ethics committee of our hospital. Allergic rhinitis was characterized by:

- 1) clinical history of nasal symptoms during natural exposure to allergen
- 2) positive skin prick tests to mixed grass pollen or *Dermatophagoides pteronyssinus* (Stallergènes, France).

Study design

This was a double-blind, randomized, crossover, placebo-controlled study with three treatment periods separated by a washout period of 10 days. During each period, on two different days separated by 4–7 days, subjects took either cetirizine (10 mg), loratadine (10 mg), or a matched placebo. Treatment efficacy was measured 1.5 or 4 h after intake by a nasal challenge test with histamine.

Histamine nasal challenge test

Histamine from stock solutions in phosphate-buffered saline (PBS), pH 7, was diluted in saline and/or distilled water/saline to obtain three histamine isotonic solutions of 0.04, 0.16, and 0.64 mg histamine per 100 μ l.

Initial NAR was measured. Vehicle (PBS in saline, pH 7, 300 mosmol) and successive increasing doubling doses of histamine (0.04, 0.08, 0.16, 0.32, 0.64, and 1.28 mg) were nebulized into each nostril with a nebulizer delivering 100 ± 3 μ l at each actuation (Stallergènes, Paris, France).

The obstructive response to histamine was assessed by measurement of NAR 1.5, 3, 5, and 7.5 min after each dose by posterior rhinomanometry (2, 19–22). Briefly, the technique consisted of measurement of the following:

- 1) nasal airflow by a pneumotachograph (Fleish no. 1) connected to a differential pressure transducer (Validyne MP 45-1-1871) placed on a mask covering the nose

- 2) pressure into the oropharynx with an identical differential pressure transducer, measured at the tip of a catheter placed over the tongue.

Transnasal pressure was the difference between pressures in the mask and into the oropharynx. Airflow and transnasal pressure were recorded on a microcomputer, leading to linear regression of nasal airway resistance as a function of airflow (Mediprom, Paris, France). NAR was finally calculated at an airflow of $150 \text{ ml} \cdot \text{s}^{-1}$.

Expression of results and statistical analysis

NAR was expressed as $\text{cmH}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}$. The maximal measurable nasal obstruction was $30 \text{ cmH}_2\text{O} \cdot \text{l}^{-1} \cdot \text{s}$. On each dose of histamine, the highest NAR was chosen to construct the dose-response curve. Individual dose-response curves to histamine with cetirizine, loratadine, and placebo were determined. Mean $\text{NAR} \pm \text{SEM}$ were calculated from individual results for each dose of histamine and each time and treatment. A repeated-measures analysis of variance (STATITCF 1994, ITCF, Paris, France) was used to compare curves between treatments. Significant differences were analyzed by a multiple-comparison procedure (Newman-Keuls test). A *P* value of less than 0.05 was considered significant.

Results

Basal NAR were similar within and between patients for all times (1.5 and 4 h) and treatments (cetirizine, loratadine, and placebo), showing that the two antihistamines had no effect on basal NAR, and confirming that the patients were free of symptoms at the time of the study.

Effect of histamine

Nasal administration of histamine induced a dose-dependent increase in NAR in patients with allergic rhinitis. As previously described, the increase in NAR was short-lived and returned to, or almost to, baseline within 10 min between each dose (2). With placebo, good reproducibility of the response to histamine at 1.5 and 4 h was observed in each patient. The mean dose-response curves with placebo were superimposed (Figs. 1 and 2), allowing statistical analysis of the curves with treatments (placebo, cetirizine, and loratadine). However, individual dose-response curves scattered on a large scale when patients were on placebo.

Effect of antihistamines

Effect at 1.5 h after intake. Fig. 1 shows the mean histamine dose-response curves obtained 1.5 h after

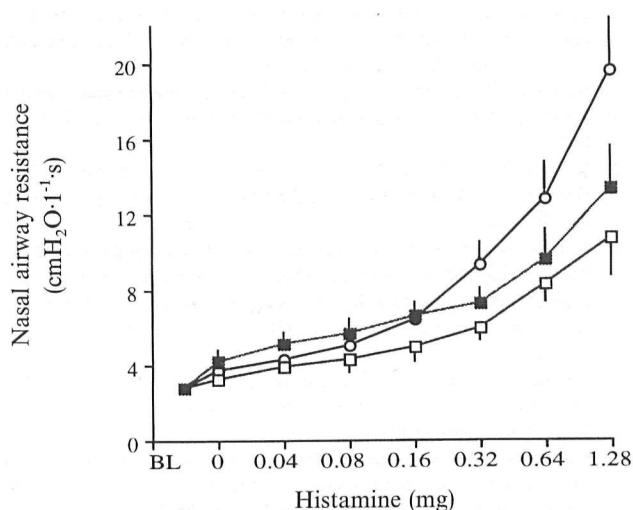


Fig. 1. Dose-response curves to histamine on nasal airway resistance 1.5 h after intake of either loratadine (closed squares), cetirizine (open squares), or placebo (open circles) in patients with allergic rhinitis. Histamine was applied onto nasal mucosa, and nasal airway resistance was measured by posterior rhinomanometry. Values are means $\pm$ SE (bars) of 12 experiments. BL: baseline.

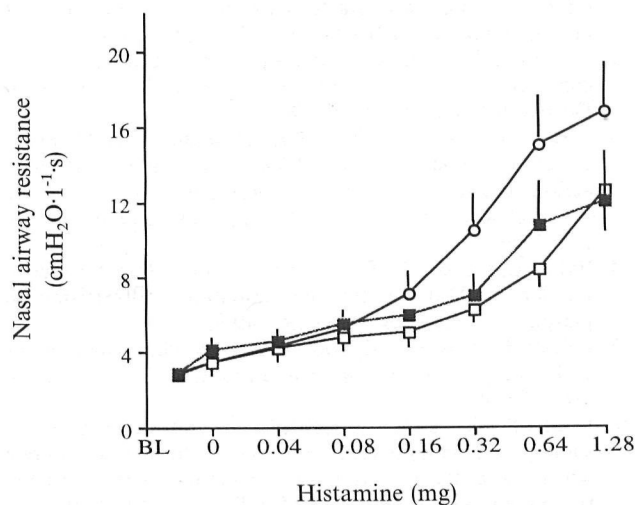


Fig. 2. Dose-response curves to histamine on nasal airway resistance 4 h after intake of either loratadine (closed squares), cetirizine (open squares), or placebo (open circles) in patients with allergic rhinitis. Histamine was applied onto nasal mucosa, and nasal airway resistance was measured by posterior rhinomanometry. Values are means $\pm$ SE (bars) of 12 experiments. BL: baseline.

intake of cetirizine, loratadine, or placebo. Cetirizine and loratadine lowered the increase in NAR caused by histamine compared with placebo for each of the 12 patients of the study. The mean response to histamine was significantly reduced for both cetirizine and loratadine as compared with placebo. However, the mean NAR for cetirizine was significantly lower than for loratadine ($P < 0.05$).

Effect at 4 h after intake. Fig. 2 shows the mean histamine dose-response curves obtained 4 h after intake of cetirizine, loratadine, or placebo, corresponding to the maximal inhibitory effect of the antihistamines used as a control. Cetirizine and loratadine lowered the increase in NAR caused by histamine compared with placebo for each of the 12 patients of the study. The mean response to histamine was significantly reduced for both cetirizine and loratadine as compared with placebo ($P < 0.05$). Moreover, the curves with cetirizine and loratadine were almost interchangeable, showing an identical effect for both antihistamines 4 h after intake.

Discussion

This study carried out in asymptomatic patients with allergic rhinitis showed a significant nasal antihistaminic effect of both cetirizine and loratadine 1.5 and 4 h after intake. This was determined by measurement of the increase in NAR induced by histamine administered at increasing doubling doses. The inhibitory effect of cetirizine was significantly greater than that of loratadine 1.5 h after intake, whereas the effects of the two antihistamines were similar 4 h after intake, indicating their similar maximal effect.

This study established two major points. First, baseline NAR was similar between all study days in the 12 patients for the three periods of treatment (cetirizine, loratadine, and placebo) and for the two times of assessment (1.5 and 4 h). This clearly indicates that all subjects were asymptomatic at the time of the study and throughout the experiment. This allows comparison of the obstructive responses induced by histamine without any artifact due to a difference in baseline. Second, our method of determining NAR by posterior rhinomanometry, which was previously carefully validated by our group (2, 19–21), has been confirmed in this study by the reproducibility of the dose-response curves observed with placebo in each patient.

We compared the nasal effect of cetirizine and loratadine at therapeutic dosage (10 mg). By 1.5 h after intake, a significant antihistaminic effect was observed in the nose both for cetirizine and loratadine as compared with placebo. This agrees with the effect of cetirizine described in the skin, where suppression of the cutaneous wheal response to histamine was already significant 0.5 h after oral intake of 10 mg of cetirizine and 1 h after intake of 10 mg loratadine (17, 18), although Simons et al. (23) described a significant effect of loratadine only 4 h after intake. However, in our study, the effect of cetirizine was significantly

more important than that of loratadine 1.5 h after intake. This agrees with the results reported by Day et al. (24), showing a more rapid onset of action for cetirizine than for loratadine, in a curative study during prolonged nasal exposure to allergen in patients with allergic rhinitis. This also agrees with the results of Simons et al. (23) in the skin, where loratadine had a slower onset of action than cetirizine, whose effect was already significant 0.7 h after intake. Finally, this result agrees with most results reported for the cutaneous effect of cetirizine in comparison with loratadine (25–27). Hence, in the nose also, a more rapid onset of action of cetirizine than loratadine is observed in patients with allergic rhinitis. This suggests that the antihistaminic effect of cetirizine is of more rapid onset than that of loratadine in the noses of patients with allergic rhinitis. Such a rapid onset of action for cetirizine may result from the rapid absorption of the drug, which becomes active without metabolism.

By 4 h after intake, the nasal effect of both antihistamines was maximal at a plateau of effect. Since the curves obtained for cetirizine and loratadine were similar, an identical maximal effect of both antihistamines occurred. This conflicts with the results observed in the skin by Simons et al. (23), showing a better effect of cetirizine than loratadine on wheal and flare reactions at 4 h. In the skin, the maximal effect obtained after intake of a single dose of cetirizine or loratadine occurred only after 4–5 h. In the nose, an almost maximal effect of cetirizine at 1.5 h after intake agrees with the results observed in clinical studies and in controlled studies with allergen (24).

In conclusion, our study showed a significant nasal antihistaminic effect of both cetirizine and loratadine 1.5 and 4 h after intake. At the plateau of effect 4 h after intake, a similar inhibition induced by both cetirizine and loratadine was observed. However, the effect of cetirizine was significantly more important than that of loratadine at 1.5 h, suggesting a more rapid onset of action of cetirizine than loratadine in the noses of patients with allergic rhinitis.

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