Allergy 2001: 56: 339–343
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ALLERGY
ISSN 0105-4538

Short communication

Effect of cetirizine, levocetirizine, and dextrocetirizine on histamine-induced nasal response in healthy adult volunteers

Background: Cetirizine, an effective H_1-receptor antagonist, is a racemate mixture of two enantiomers: levocetirizine (*R* enantiomer) and dextrocetirizine (*S* enantiomer).
Methods: To investigate the pharmacologic activity of the two enantiomers of cetirizine, we conducted a randomized, double-blind, four-way, crossover study to assess the effect of treatment with 5 mg levocetirizine, 5 mg dextrocetirizine, and 10 mg cetirizine and matched placebo, on histamine-induced changes in the nasal airways of 24 healthy volunteers. Four hours after a single oral intake, all subjects were challenged by nasal aerosol application with increasing doubling concentrations (from 0.25 to 32 mg/ml) of histamine in both nostrils. Nasal resistance was measured by passive anterior rhinomanometry (PAR), and changes in histamine threshold were calculated together with the absolute number of sneezes after each challenge.
Results: Both levocetirizine and cetirizine significantly attenuated the histamine-induced increase in nasal airway resistance by nearly 50% (from a median resistance of 2.51 Pa per cm^3/s to 1.29 and 1.31 Pa per cm^3/s, respectively) at the maximal concentration, and they concomitantly increased the histamine threshold by fourfold (from 8 to 32 mg/ml), compared with placebo. Sneezing was also attenuated by both levocetirizine and cetirizine. However, these antihistaminic effects were not seen with dextrocetirizine.
Conclusions: This study shows a similar activity of levocetirizine and cetirizine on the inhibition of histamine-induced increase in nasal resistance, indicating that the antihistaminic properties of cetirizine are probably attributable to levocetirizine.

D. Y. Wang[1], F. Hanotte[2], C. De Vos[2], P. Clement[3]
[1]National University of Singapore, Singapore; [2]UCB Pharma, Brussels, Belgium; [3]Academisch Ziekenhuis, ENT Department, Vrije Universiteit Brussel, Brussels, Belgium

Key words: cetirizine; dextrocetirizine; histamine threshold; levocetirizine; nasal resistance.

Christine De Vos, PhD
UCB Pharma
Allée de la Recherche 60
B-1070 Brussels
Belgium

Accepted for publication 23 November 2000

The role of histamine has been well documented in the pathophysiology of allergic airway diseases (1–3). An increased understanding, over the last few decades, of the pathogenic role of histamine in allergic diseases has been associated with the development of specific and highly efficacious H_1-receptor antagonists for symptomatic relief of allergic disease, particularly seasonal and perennial allergic rhinitis and urticaria (4–6). The H_1-receptor antagonists, generally called antihistamines, have broadly been classed into two categories, the first- and second-generation antihistamines. The first-generation antihistamines have been associated with central nervous system and anticholinergic side-effects, particularly sedation and impaired psychomotor activity (7), and are therefore not much used currently. In contrast, the newer second-generation antihistamines, such as cetirizine, loratadine, and fexofenadine, exhibit fewer sedative and anticholinergic effects and have a rapid onset of action, making them ideal for symptomatic relief of the allergic disease.

Controlled trials in patients with seasonal and perennial rhinitis have demonstrated that cetirizine is effective in attenuating nasal and/or ocular symptoms resulting from experimental or natural allergen exposure (8–11). However, cetirizine is a racemate mixture of two enantiomers: levocetirizine (*R* enantiomer) and dextrocetirizine (*S* enantiomer). The aim of this study was to investigate the activity of these two enantiomers on histamine-induced changes in nasal resistance and sneezing in healthy volunteers, and then to compare these effects with those of cetirizine and placebo.

Material and methods

Subjects

Twenty-eight healthy nonallergic volunteers were enrolled in this study. Of them, 24 subjects (nine males and 15 females) aged 20–38 years (mean age 29 years) completed the study. They were symptom-free and had normal findings on routine hematologic and biochemical blood test parameters. None of the volunteers smoked

more than five cigarettes a day or had a history of allergy or hypersensitivity to piperazines. They did not take any medication, except oral contraceptives during the 2 weeks preceding enrollment. All volunteers gave written informed consent prior to the study. This study was approved by the ethics committee of the university hospital, Free University of Brussels (Academisch Ziekenhuis, Vrije Universiteit Brussel), Belgium.

Study design

This was a randomized, double-blind, placebo-controlled, four-way, crossover study. Each volunteer was entered into a randomized schedule to receive a single dose of 5 mg levocetirizine, 5 mg dextrocetirizine, 10 mg cetirizine, and matched placebo. Four hours after each intake, all subjects were challenged by nasal aerosol application with increasing doubling concentrations (from 0.25 to 32 mg/ml) of histamine in both nostrils. Nasal airway resistance was measured by passive anterior rhinomanometry (PAR), and changes in histamine threshold (concentration that induces 100% increase in unilateral nasal resistance at the baseline) were calculated together with the absolute number of sneezes after each challenge.

To minimize the influence of the existing conditions of nasal obstruction and nasal hyperresponsiveness to the control solution, a standardized protocol for PAR and histamine challenge was maintained throughout all visits (12, 13). An inclusion criterion was applied to all volunteers who had a baseline nasal airway resistance of <2.8 Pa per cm^3/s that did not increase by more than 30% from baseline value after application of the control solution. Nasal challenges with control solution and increasing doubling concentrations of histamine were then performed. Volunteers who demonstrated a 100% increase in nasal resistance at histamine concentrations of <8 mg/ml were randomized to receive the study medication. In our experience, most healthy volunteers are eligible by this criterion. If the volunteers were disqualified by this criterion at any treatment visit, they were withdrawn from this study.

Volunteers were assessed for general well-being and any adverse events before and after nasal provocation, and, all being well, they were given appointments to attend the clinic for the next visit after a washout period of 7–14 days.

Measurement of nasal resistance

Nasal resistance was measured by PAR (Heyer, Bad Ems, Germany), as previously described (14). Briefly, a fixed airflow of 250 cm^3/s was blown through a nozzle into one nostril. The pressure induced by the nasal airway resistance to this airflow at a given level of the nozzle was measured. The measurements were expressed in Pa per cm^3/s, as recommended by the International Committee on Standardization of Rhinomanometry (15). In this study, nasal airway resistance was measured in each nostril 1 min and 5 min after each challenge, and the mean value of the two time measurements was calculated. The higher value of mean resistance from one of the nostrils was subsequently used in the final efficacy analysis.

Histamine nasal provocation test

Histamine solutions of 0.25, 0.5, 1, 2, 4, 8, 16, and 32 mg/ml were purchased (from HALAB Allergy Service, Brussels, Belgium) and equilibrated at 30°C. The control solution (diluent of histamine solution) was composed of ε-aminocaproic acid (EACA; 13.1 mg), disodium phosphate (9.1 mg), sodium phosphate (1.2 mg), human serum albumin (HSA; 0.3 mg), and phenol (5 mg) in 1.0 ml water for injection.

Nasal provocation was carried out by nasal aerosol application with a Heyer nebulizer (Heyer, Bad Ems, Germany) (12, 13). The nebulizer contained the challenge solution and was aerosolized for introduction into the volunteer's nostrils through a nozzle. The nasal mucosa was consecutively provoked six times for 10 s (three times for each nostril alternately), with the study subject being in complete apnea after a full inspiration, in order to prevent the provocation solution from entering the bronchial tree. The same challenging procedures with increasing concentrations of histamine were

Table 1. Comparison of effect of treatment for 4 h with 10 mg cetirizine, 5 mg levocetirizine, and 5 mg dextrocetirizine compared with placebo on histamine-induced changes in nasal airway resistance (unit = Pa per cm^3/s; $n=24$ healthy volunteers)

	Nasal airway resistance Pa per cm^3/s				
Histamine concentration (mg/ml)	Placebo (median)	Cetirizine (median)	Levocetirizine (median)	Dextrocetirizine (median)	Friedman test[1] P
1	0.78	0.79	0.76	0.84	0.831
2	0.94	0.83	0.83	0.94	0.099
4	1.12	0.88	0.87	1.12	0.047
	+([2])				
8	1.44	1.01	1.11	1.26	0.031
	*				
16	1.82	1.14	1.17	1.36	0.002
	***				
		**			
			*		
32	2.51	1.31	1.29	2.06	0.002
	**			*	
		**			

[1]Global evaluation with Friedman test.
[2]When global evaluation was statistically significant ($P<0.05$), two-by-two comparison of treatment was done. Only comparisons with $P\leq 0.10$ are mentioned in tables:
$^{+}0.05<P<0.10$
$^{*}0.025<P<0.05$
$^{**}0.01<P<0.025$
$^{***}0.001<P<0.01$.

Table 2. Comparison of effect of treatment for 4 h with 10 mg cetirizine, 5 mg levocetirizine, and 5 mg dextrocetirizine compared with placebo on histamine threshold concentration, based on frequency of volunteers demonstrating 100% increase in mean nasal resistance ($n=24$ healthy volunteers)

	Number of volunteers			
Histamine threshold concentration (mg/ml)	Placebo	Cetirizine	Levocetirizine	Dextrocetirizine
0.5	0	1	0	1
1	1	0	2	3
2	6	1	0	2
4	4	0	1	1
8	5	5	2	6
16	1	2	3	2
32	5	5	5	5
>32	2	10	11	4
Median of histamine threshold concentration	8	32	32	8

Results of comparisons
Statistics were done on difference between logarithms (in base 2) of threshold concentration between each pair of treatments. For these calculations, threshold of >32 was replaced by 64 mg/ml.
Friedman test
Global evaluation $P=0.001$
Two-by-two comparisons
Levocetirizine *vs* dextrocetirizine $0.025<P\leq0.05$
Levocetirizine *vs* cetirizine $P>0.10$
Levocetirizine *vs* placebo $0.01<P\leq0.025$
Dextrocetirizine *vs* cetirizine $0.05<P\leq0.10$
Dextrocetirizine *vs* placebo $P>0.10$
Cetirizine *vs* placebo $0.025<P\leq0.05$.

performed, allowing an interval of 1 min after the last PAR measurement (which was 5 min after the beginning of the previous histamine administration).

Statistical analysis

The sample size was estimated by a power calculation done on the basis of a previous study (data on file). On this basis, it was estimated that, after treatment with active drug, at least 24 volunteers were required to detect a significant doubling in histamine threshold at 90% power level with an alpha error of 5%; consequently, 28 eligible individuals were recruited into the study to allow for dropouts.

All data were expressed as median values, and the overall significance of changes in histamine threshold, nasal resistance, and the number of sneezes resulting from any treatment was assessed by the Friedman test. Multiple comparisons between all pair treatments were performed with the normal approximation of the multiple comparison procedure based on the Friedman rank sums test (16). All statistical tests were performed with the SAS® statistical package (Version 6.08) on an IBM-compatible microcomputer. Two-sided tests were used, and values of $P<0.05$ were regarded as significant.

Results

Of the 28 volunteers recruited into the study, results for four subjects were not included in the overall efficacy analysis. One subject suffered from an episode of bronchitis after visit 4 and prior to receiving the last treatment at visit 5, and therefore did not complete the entire study protocol. The other three subjects, despite the fact that they were eligible, failed to react to histamine, showing a histamine threshold concentration of >32 mg/ml at every treatment visit. Their results were therefore considered to be not evaluable, and these volunteers were replaced.

Effect of treatment on nasal resistance

Measurement of nasal airway resistance under placebo demonstrated that this was increased by histamine administration in a dose-dependent manner (Table 1). Treatment with both cetirizine and levocetirizine significantly attenuated the histamine-induced increases in nasal airway resistance at the maximal concentration of 32 mg/ml with almost 50% reduction over placebo (Table 1). Both cetirizine and levocetirizine were found to attenuate significantly the effects of histamine at concentrations of ≥8 and ≥16 mg/ml, respectively. In contrast, treatment with dextrocetirizine did not show any significant effect on histamine-induced increase in nasal airway resistance as compared to placebo.

Effect of treatment on histamine threshold concentration

After treatment with placebo, 16/24 (67%) subjects demonstrated a histamine threshold concentration of ≤8 mg/ml. Treatment with cetirizine, levocetirizine, and dextrocetirizine decreased the number of subjects demonstrating a histamine threshold concentration of ≤8 mg/ml to 7/24 (29%), 5/24 (21%), and 13/24 (54%), respectively. The histamine threshold concentration was significantly increased fourfold from a median value of 8 mg/ml after treatment with placebo to a median value of 32 mg/ml after treatment with cetirizine ($P<0.05$) or levocetirizine ($P<0.025$) (Table 2). In contrast, dextrocetirizine was not found to alter significantly the histamine threshold concentration as compared to placebo, as the number of subjects with a threshold concentration below 8 mg/ml was 13 out of 24. Levocetirizine was found to be significantly

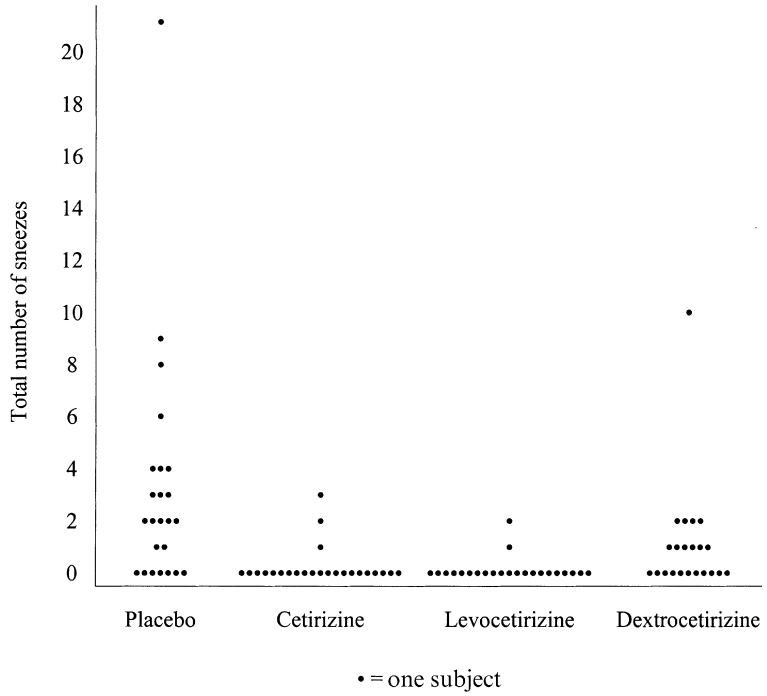

Figure 1. Effect of treatment for 4 h with placebo, 10 mg cetirizine, 5 mg levocetirizine, and 5 mg dextrocetirizine on histamine-induced sneezes.

($P<0.05$) more effective than dextrocetirizine in increasing the histamine threshold concentration. A comparison between cetirizine and levocetirizine, however, did not show a significant difference between them (Table 2).

Effect of treatment on sneezing

Fig. 1 shows the effect of individual treatment on the number of sneezes induced by histamine challenge. Treatment with either cetirizine or levocetirizine significantly ($P<0.01$) reduced histamine-induced sneezes, but not treatment with dextrocetirizine as compared to placebo ($P>0.10$).

Evaluation of safety

There was no special report on health-related problems or discomfort (i.e., drowsiness, fatigue, and dry mouth) caused by study medications among the volunteers. Only one subject reported an adverse event of bronchitis, which occurred 8 days after treatment with levocetirizine and was not judged to be a direct result of the study drug. However, this was a single-dose study, and the volunteers were interviewed 4 h after each intake of the study medication.

Discussion

In this study, levocetirizine 5 mg and cetirizine 10 mg appeared to be comparable in their antihistaminic activity. They significantly attenuated histamine-induced increases in nasal airway resistance by almost 50% over placebo at the maximal concentration of 32 mg/ml. Concomitantly, the histamine threshold concentration was increased fourfold from 8 to 32 mg/ml. The number of sneezes induced by histamine nasal provocation was also significantly decreased by treatment with cetirizine or levocetirizine. In contrast, treatment with dextrocetirizine did not show a similar 'protective' effect as compared to placebo.

Our findings are in accordance with the findings of several studies investigating the effects of cetirizine in patients with seasonal and perennial allergic rhinitis. Frossard et al. have recently conducted two studies to investigate the effects of treatment with 10 mg cetirizine on changes in the nasal airway resistance of asymptomatic seasonal allergic rhinitics challenged with increasing doubling doses of histamine (17, 18). These authors showed that cetirizine significantly attenuated histamine-induced increases in nasal airway resistance (NAR) only 1.5 h after administration (17), and that these effects were prevalent even 24 h after treatment (18), when compared with placebo.

This is the first study to investigate the specific effects of each enantiomer of cetirizine on the histamine-induced nasal response. In view of the similarity of the antihistaminic effects observed for cetirizine and levocetirizine and the lack of any significant effects for dextrocetirizine in this study, it is likely that the effects of cetirizine in the management of allergic rhinitis are due to levocetirizine. Since cetirizine is composed of equal quantities of the two enantiomers, our study suggests that

preparations of levocetirizine at a dose of 5 mg may be useful in the management of seasonal and perennial allergic rhinitis in the future. In addition to its antihistaminic property, levocetirizine at the single dose of 5 mg was well tolerated by the volunteers, who did not suffer from any side-effects in this study.

In conclusion, this study demonstrates that the antihistaminic properties noted for cetirizine in the management of seasonal and perennial allergic rhinitis are probably due to the levocetirizine enantiomer. Further studies are required to substantiate these findings in patients with ongoing seasonal and perennial allergic rhinitis.

Acknowledgments

We thank Marie-Paule Derde and Léon Kaufmann of DICE and VUB, Brussels, Belgium, as well as Christian Otoul of UCB-Pharma, for bringing us their expertise in biostatistics. We also thank Pascale Segers for preparing the figures. This study was sponsored by UCB-Pharma, Brussels, Belgium.

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