

Dose-ranging, placebo-controlled study of cetirizine nasal spray in adults with perennial allergic rhinitis

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A total of 360 patients with perennial allergic rhinitis were randomized in a placebo-controlled, dose-finding study comparing three concentrations (0.06%, 0.125%, and 0.25%) of a cetirizine nasal spray, administered three times a day for 2 weeks. The primary criterion of efficacy was the percentage of days with no or only mild symptoms of rhinitis (PDMax1), as evaluated by the patients. The median PDMax1 were 16.7%, 30.8%, 42.9%, and 26.7% for the placebo, 0.06%, 0.125%, and 0.25% groups, respectively. Although the global comparison among the four groups only approached statistical significance ($P = 0.076$), the difference (26.2%) between the placebo and 0.125% groups was clinically and statistically significant ($P = 0.011$). For the global evaluation by the investigator, the best results were seen in the 0.125% group ($P = 0.03$). The occurrence of adverse events did not differ among the four treatment groups and consisted mainly of nasal events, occurring in 22.5%, 17.1%, 12.9%, and 24.4% of the patients for the placebo, 0.06%, 0.125%, and 0.25% groups, respectively ($P = 0.184$). These results indicate that the 0.125% concentration is significantly better than placebo and offers the best therapeutic ratio.

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Allergic rhinitis is the most common form of atopic disease and has an estimated prevalence of 5–22% (5). Beside avoidance of the causal allergen, the basic therapeutic approach in patients suffering from allergic rhinitis is the administration of antihistaminic (H_1 -antagonists) agents (5). Cetirizine is one of the second-generation H_1 -antagonists (1, 4). The concept of nasal administration of H_1 -antagonists is attractive. Theoretically, this administration modality could increase the therapeutic effect (6). Cetirizine retains its pharmacologic properties after nasal administration and is well tolerated at concentrations up to 0.25% (2). On these grounds, a dose-ranging, placebo-controlled trial was conducted to study the efficacy, safety, and dose-effect relationship of cetirizine after nasal administration.

Material and methods

Patients

Male and female patients aged 12–65 years were admitted to the study. Women had to follow a con-

traceptive method. Perennial allergic rhinitis had to be known for at least 1 year and to be documented by skin test, RAST, or both. Nasal congestion, sneezing, and rhinorrhea were scored according to a 4-point scale: 0 = absent, 1 = mild, 2 = moderate, and 3 = severe. The sum of the scores for the three symptoms had to be ≥ 5 .

The following conditions were considered to be exclusion criteria: presence of a seasonal allergen to which the patient was allergic; infection of the upper respiratory airways during the 3 weeks before study entry; forbidden prior medications (the duration in parentheses indicates the duration of the washout period): astemizole (6 weeks), systemic glucocorticoids (2 weeks), ketotifen or glucocorticoids by nasal or ocular route (1 week), and nasal or ocular sodium cromoglycate or decongestants or H_1 -antagonists (2 days). Desensitization was allowed, except in ascending phase. Patients had to be free of concomitant ears, nose, and throat disorders and other clinically relevant systemic diseases. Pregnant or lactating women were excluded.

Randomization and treatment

Patients were randomized into four groups according to lists prepared in blocks and stratified by center. Blinding was maintained until all data were entered into the database and validated. Patients received in each nostril a spray of 100 µl of a placebo or cetirizine solution at the concentrations of 0.06%, 0.125%, or 0.25%, respectively, three times a day. Trial medication was scheduled to be given for two periods of 7–11 days each. Concomitant medications listed above were not allowed during the study, except inhaled corticosteroids at a dose ≤ 400 µg/day and inhaled sodium cromoglycate.

Patients were allowed to leave the study in case of inefficacy, adverse events, major protocol violation, or personal inconvenience.

Clinical and laboratory assessments

Patients were seen at study entry, at midstudy, and at study end. Complete history and physical examination were recorded at entry, and nasal examination and anterior rhinoscopy at each visit. A global evaluation of the treatment efficacy was made by the investigator at the final visit, using a 5-point scale: worsening, no change, slight improvement, good improvement, and excellent improvement. Each patient kept a daily record card to score rhinitis symptoms with the same 4-point scale as that used by the investigator.

For safety, at each visit, patients were questioned about the occurrence of anything unusual with regard to their health. In case of a positive answer, the nature, incidence, severity, duration, and relationship of the adverse event to the study medication were described. Adverse events were classified according to the COSTART dictionary (*Coding symbols for thesaurus of adverse reaction terms*, Department of Health and Human Services, Rockville, MD, USA, 1989, 3rd ed). Blood tests (blood count, SGOT, SGPT, gamma-GT, bilirubin, and creatinine) were done at the first and last visits.

Statistical considerations

The target enrollment was 360 patients (90/group). This number was calculated to detect an absolute difference $\geq 20\%$ between the mean percentages of days with no or only mild symptoms (PDMax1) (see below) for the four groups, with an α error of 5% and a β error of 20%. The primary efficacy criterion was the percentage of days with a maximal four-symptom score ≤ 1 (PDMax1); this percentage was obtained for each patient in the following manner. Every day, a maximal four-symptom score, corresponding to the highest score for the four rhinitis symptoms from

the daily record card, was defined. The maximal four-symptom score was then used to calculate the percentage of days with a maximal four-symptom score ≤ 1 . The percentage of days with a maximal four-symptom score equal to 0 (PDMax0) or ≤ 2 (PDMax2), scores of rhinitis assessed by the investigator, rhinoscopy, and the overall assessment of the treatment efficacy were secondary efficacy criteria.

Analyses were performed on all randomized patients (intention-to-treat principle). The Cochran-Mantel-Haenszel test (CMH), based on ranks, and stratified for disease severity at base line, was used. For each efficacy variable, a global comparison of the four treatment groups was made. If the difference was significant at the level of 10%, comparisons between pairs of treatment groups were done. All tests were two-tailed, with a level of significance of 5%, except for the pairwise comparisons, where the 2% level was used to take the multiplicity of tests into account.

Ethical considerations

The study was conducted according to the Declaration of Helsinki and to the principles of good clinical practice and with the authorization of the ethical committees of the participating institutions. Patients had to give their informed consent; for patients under 18 years of age, consent of the parents was required.

Results

A total of 360 patients were randomized: 89 in the placebo group, 88 in the 0.06% group, 93 in the 0.125% group, and 90 in the 0.25% group. Patients entered the study from October 1990 until April 1992 with an interruption from May until September 1991; entrance rates were comparable for the four groups of patients (data not shown).

The main demography and disease characteristics are presented in Table 1. The four groups were very similar in terms of sex, age, and duration of rhinitis. All patients had documented allergy for a perennial allergen. Prior medication exposure, disease severity (evaluated by the patients and by the investigators), and rhinoscopic findings were similar among the four groups.

Protocol adherence

The median number of days of treatment was 7 for both periods without significant difference among the four treatment groups. The median compliance was 100% in period 1 and 98% in period 2, without significant difference among the four treatment

Table 1. Demographic and disease characteristics

		Placebo n=89	0.06% n=88	0.125% n=93	0.25% n=90
Sex (%)	M	49	41	45	47
	F	51	59	55	53
Age (years)	Median	26	27	28	27
	Min-max	12-58	12-62	13-67	12-68
Allergy	Any perennial allergen	89	88	93	90
	House-dust mites	80	83	88	81
	House dust	54	49	55	50
Duration of rhinitis (years)	Median	6	5	4	5
	Range	1-27	1-32	1-42	1-31
Prior administration of drugs	H ₁ -antagonists (except astemizole and ketotifen)	43	48	35	43
	Astemizole	4	1	7	3
	Ketotifen	0	1	4	1
	Corticosteroids	19	25	25	32
	Sodium cromoglycate	13	11	11	6

groups. A total of 332 (92%) of the patients completed the study. Fourteen patients were withdrawn prematurely for inefficacy *or* for an adverse event: eight in the placebo group, one in the 0.06% group, three in the 0.125% group, and two in the 0.25% group.

Efficacy analyses

All symptoms assessed by the patients improved progressively in all treatment groups, including the placebo group. However, the improvement was greatest in the 0.125% group, intermediate in the 0.06 and 0.25% groups, and lowest in the placebo group. PDMax scores are presented in Table 2. None of the comparisons reached statistical significance for PDMax0 and PDMax2. For PDMax1, the global comparison between the four groups approached statistical significance (CMH test; $P = 0.076$). The comparison between the 0.125%

Table 2. Median PDMax for patients included in intention-to-treat population (mean $\pm$ SD)

Group	n	PDMax0	PDMax1	PDMax2
Placebo	87	0	16.7	84.6
		(2.1 $\pm$ 6.0)	(27.4 $\pm$ 30.5)	(68.5 $\pm$ 34.0)
0.06%	87	0	30.8	92.3
		(4.3 $\pm$ 12.7)	(35.5 $\pm$ 31.7)	(77.6 $\pm$ 30.5)
0.125%	91	0	42.9	92.3
		(4.0 $\pm$ 10.6)	(40.1 $\pm$ 34.7)	(76.7 $\pm$ 31.7)
0.25%	89	0	26.7	87.5
		(3.8 $\pm$ 10.6)	(32.0 $\pm$ 32.5)	(76.0 $\pm$ 31.4)

group and the placebo group was statistically significant (CMH test; $P = 0.011$), whereas the differences between the placebo group and the two other groups was not significant.

The investigator's evaluation of rhinitis symptoms and rhinoscopic variables also showed an improvement in all groups, without significant difference (data not shown). Results of the global evaluation by the investigator are displayed in Fig. 1: they were clearly best in the 0.125% group ($P = 0.03$). Intermediate results were obtained in the 0.06% ($P = 0.387$) and 0.25% ($P = 0.08$) groups.

Safety analysis

The occurrence of adverse events is shown in Table 3. The occurrence of any adverse event did not differ statistically among the four treatment groups

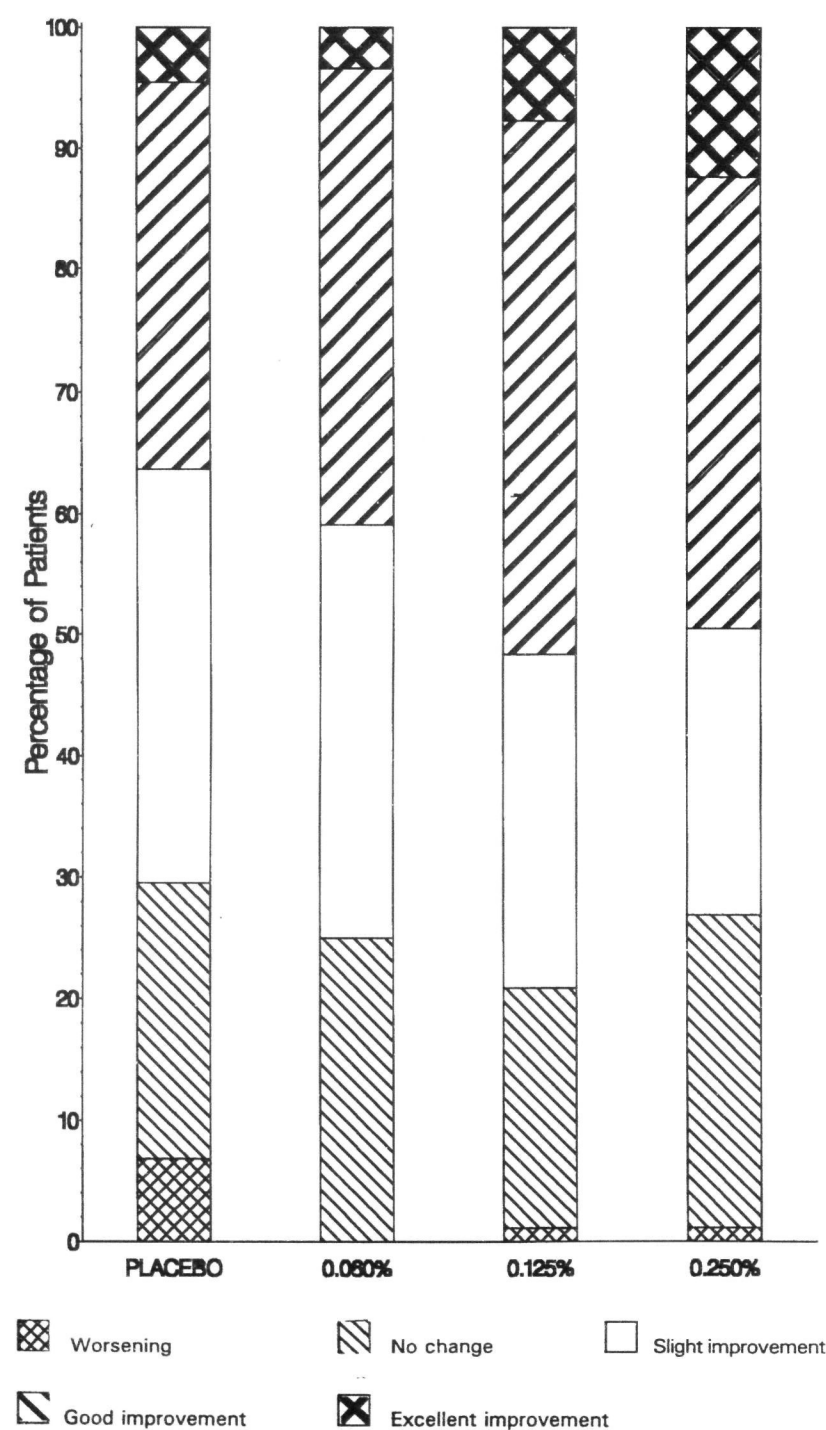


Fig. 1. Global evaluation of treatment by investigator.

Table 3. Percentage of patients with adverse events*

Body system	Group			
	Placebo n=89	0.06% n=88	0.125% n=93	0.25% n=90
Any	42	35	31	42
Body as a whole	15	16	15	22
Cardiovascular	0	0	0	1
Digestive	5	1	5	3
Hemic/lymphatic	2	0	1	0
Metabolic/nutritional	1	0	4	2
Musculoskeletal	0	1	1	1
Nervous	3	2	3	2
Respiratory	27	23	15	27
Skin/appendages	1	3	3	2
Special senses	0	3	7	1

* Based on all patients who received at least one dose of trial medication. Patients who developed more than one adverse event in given body system were counted once for that body system.

($P = 0.354$; CMH test). In the category "respiratory", the occurrences of rhinitis, epistaxis, or both were 22%, 17%, 13%, and 24% of the patients in the placebo, 0.06%, 0.125%, and 0.25% groups, respectively ($P = 0.184$; CMH test). The term "rhinitis" had been mainly used by the investigator for nasal burn or nasal inflammation. Only two patients, one each in the 0.125% and 0.25% groups, developed mild somnolence. Most of the adverse events were mild to moderate. There was no significant modification of the laboratory variables.

Discussion

This study shows that cetirizine administered as a nasal spray at the concentration of 0.125% was statistically and clinically better than placebo in patients with perennial allergic rhinitis. This conclusion is based on the analysis of the principal criterion of analysis for the study, i.e., the percentage of days with maximal four-symptom score ≤ 1 (PDMax1). Patients with a high PDMax1 value were those with a high percentage of days with all symptoms absent or mild: from a clinical point of view, one may consider that they had good control of their disease. Conversely, patients with a low PDMax1 value had a low percentage of days with all symptoms absent or mild, i.e., a high percentage of days with poorly controlled disease. The use of PDMax1 is supported by several considerations. First, it is derived from the symptom evaluations by patients themselves, rather than by the investigator; this is an important feature, in a disease where symptoms are largely subjective. Second, it combines all rhinitis symptoms: a patient with minimal congestion but severe rhinorrhea had a severe maximal four-symptom score; this makes sense since the worst score is likely

to dictate the overall feeling of the patient. Third, in contrast with other combined scores, such as the sum of scores at predefined time points, PDMax1 encompasses all days of treatment. Finally, PDMax1 has been used successfully in previous studies (3).

The median PDMax1 was equal to 16.7% and 42.9% in the placebo and 0.125% groups, respectively; in other words, the patients treated with the 0.125% nasal spray of cetirizine had 2.5 more days with no or only mild symptoms than the placebo patients. This represents a substantial clinical benefit. The benefit was observed in all patients, irrespectively of the severity of the disease at base line. The subjective improvement reported by the patients treated with the nasal spray of cetirizine was further supported by the global evaluation by the physician.

The second important conclusion of this study is that the effect of the nasal spray of cetirizine was dose-related. The interesting feature of the dose-effect relationship is that the therapeutic efficacy was partially lost at the highest concentration (0.25%). This resulted in a bell-shape dose-effect relationship. In the present case, this phenomenon was probably due to the increased occurrence of adverse events at the concentration of 0.25%, as discussed below. These adverse events consisted mainly of local symptoms such as nasal irritation or rhinorrhea; they could be easily confused with the symptoms of the disease itself, a fact which may explain the apparently poorer therapeutic efficacy at the 0.25% concentration.

The safety profile of the nasal spray of cetirizine was very good: overall, there was no statistically significant difference among the four treatment groups, and most adverse events were mild to moderate. The highest number of adverse events was reported in the respiratory system. Although not statistically different, the number of adverse events was clearly lowest in the 0.125% group. The highest number of nasal adverse events in the 0.25% group may reflect a truly higher incidence of adverse effects at the highest cetirizine concentration. In contrast, in the 0.06% and placebo groups, the apparently higher occurrence of nasal adverse events might be related to an insufficient control of rhinitis by the treatment and the report of disease symptoms as adverse events. Mild somnolence was observed in only two patients, one each in the 0.125% and 0.25% groups. Thus, local administration of cetirizine almost completely avoided central nervous system adverse events.

In conclusion, this study indicates that, for cetirizine nasal spray, the best therapeutic effect and the lowest rate of adverse event were achieved at the 0.125% concentration, which has been selected for further development. Issues to be addressed in the future include effect of cetirizine nasal spray in pa-

tients with seasonal allergic rhinitis, and the optimal treatment duration and number of administrations per day.

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