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Cetirizine and pseudoephedrine retard alone and in combination in the treatment of perennial allergic rhinitis: A double-blind multicentre study*

B. Bertrand[1], J. Jamart[1], J.L. Marchal[2], C. Arendt[2]

[1] Cliniques Universitaire UCL de Mont-Godinne, Yvoir, Belgium
[2] UCB SA, Pharma Sector, Research and Development, Braine-l'Alleud, Belgium

SUMMARY

We compared the efficacy and safety of 5 mg cetirizine (CTZ), 120 mg pseudoephedrine retard (PER) and their combination (COM), given twice daily for three weeks, for the treatment of perennial allergic rhinitis. Two hundred and ten evaluable patients (97 males and 113 females) were included in the study and randomly allocated to one of three treatment groups, each of 70 patients. Nasal obstruction, sneezing, rhinorrhoea, nasal and ocular pruritus were scored each day throughout the study by patients using a symptom scale ranging from 0 (no symptom) to 3 (severe). The mean proportion of days without symptoms was higher in the COM group (11.8%) than in the CTZ (6.8%) and PER (5.1%) groups, but the differences were not statistically significant. The mean percentage of days when symptoms were absent or at most mild was significantly higher in the COM group (64.8%) than in either CTZ (45.5%; p=0.003) or PER groups (40.6%; p=0.0001). In addition, evaluation of symptoms by investigators and their global evaluation at the end of treatment showed statistically significant differences in favour of COM compared, to both CTZ and PER. The most frequent adverse events were somnolence in the CTZ and COM groups (8.6% and 12.9%, respectively) while insomnia was most frequent in the PER group. No clinically significant abnormalities were found in haematological or biochemical tests. These results indicate that the combined treatment was more effective than and as well tolerated as treatment with each individual agent.

Key words: cetirizine, pseudoephedrine retard, treatment, perennial, allergic rhinitis

INTRODUCTION

Although avoidance of causal allergens remains the desirable approach to the treatment of patients with allergic rhinitis, this can rarely be adequately achieved. Consequently, drug treatment is usually necessary and H_1-antagonists are the agents of first choice. Cetirizine (CTZ) is a potent and selective second-generation antihistamine with a rapid onset and prolonged duration of action (Simons et al., 1990). CTZ is devoid of anticholinergic and anti-serotonin activity (Snyder and Snowman, 1987) and, at recommended dosage, has little sedative potential and does not impair driving performance (Gengo and Manning, 1990). Studies have shown that CTZ, in a dose of 10 mg once daily or 5 mg twice daily (Wasserman et al., 1991), is more effective than placebo and at least as effective as other second-generation antihistamines in the treatment of perennial allergic rhinitis (Berman et al., 1988; Lobadon et al., 1990).

It is well recognized that H_1-antagonists do not always provide complete relief of nasal congestion, especially when the vasomotor role is predominant. Many formulations combining an antihistamine with a nasal decongestant have therefore been developed in an attempt to provide greater efficacy. Pseudoephedrine is a well-established sympathomimetic agent in the treatment of rhinitis which can be used either alone or together with an H_1-antagonist (Connell et al., 1982). Pseudoephedrine retard-pellets (PER) are a slow-release formulation of pseudoephedrine, with a plasma half-life of 12 h, which are given in two daily doses.

We performed a multicentre, double-blind, randomised study of 3 weeks' duration comparing the effects of CTZ (5 mg b.i.d.) alone, PER (120 mg b.i.d.) alone and the combination (COM) of CTZ and PER (5 mg plus 120 mg b.i.d., respectively), in order to determine whether the combination was more effective than both single agents in the treatment of perennial allergic rhinitis.

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MATERIAL AND METHODS

Patients

A total of 210 patients with perennial allergic rhinitis, males and females aged 12–65 years, from eight centres, was included in the study. The trial was conducted in accordance with the Declaration of Helsinki and after approval of the protocol by the relevant Ethics Committees. All patients (or their parents or legal representatives if aged less than 18 years) gave written informed consent to participate in the study.

Perennial allergic rhinitis was diagnosed from a reliable history of at least one year's duration, and a positive allergy test (prick test or RAST). Pollen-sensitive patients were excluded during the pollen season. Inclusion in the study required the presence of the following three symptoms: nasal obstruction, rhinorrhoea, and sneezing. These were evaluated, together with symptoms of nasal and/or ocular pruritus, on a 4-point scale (scored as 0: no symptoms; 1: mild, symptom present but not disturbing; 2: moderate, disturbing but allowing normal activities and sleep; or 3: severe, symptom interfering with daily activities and/or sleep). Nasal obstruction had to be of at least moderate severity and the total score for nasal obstruction, rhinorrhoea and sneezing had to be at least "5", either on the day before starting (day 0) or the first day of treatment (day 1).

Wash-out periods were required for patients taking astemizole (six weeks), systemic corticosteroids, ketotifen and MAO inhibitors (two weeks), topical steroids and disodium cromoglycate (one week), and local decongestants or other antihistamines (two days). Use of any of these drugs during the trial led to exclusion. However, patients were allowed to use inhaled corticosteroids for asthma, in a maximum dose of 400 g/day, throughout the study.

Those with infectious rhinitis, obstructive nasal polyposis or a significant deviation of the nasal septum, dermatitis, infections requiring antibiotic treatment or any serious medical disorder were not included. Pregnancy, childbearing potential and breast feeding were also exclusion criteria.

Patients eligible for inclusion were allocated at random into one of three treatment groups: cetirizine 5-mg tablets (CTZ), pseudoephedrine retard 120-mg capsules (PER) or cetirizine 5-mg tablets combined with pseudoephedrine retard 120-mg capsules (COM). The "double-dummy" technique was used to ensure blindness. Patients were instructed to take one tablet and one capsule twice daily for three weeks. Treatment started on the evening of day 1 (visit 1). The study required two subsequent review visits, one between the fifth and ninth day of treatment (visit 2) and the other at the end of treatment (visit 3).

Symptoms were evaluated by the investigator, as described above, on entry to the study and at visits 2 and 3. Patients were asked to complete, each evening throughout the study, a diary card in which they recorded each symptom (blocked nose, sneezing, runny nose, itchy nose, itchy eyes) using the same 4-point scale as the investigator. In addition, the investigator made a global evaluation at visit 3, using a 5-point scale (0: worse; 1: no change; 2: slight improvement; 3: marked improvement; 4: excellent improvement, patient symptom-free).

All reported adverse events were recorded and rated for severity, duration and possible relationship to study medication. Events were classified according to Costart (1989). A full blood analysis (haemoglobin, haematocrit, erythrocytes, total and differential white blood cell count, SGPT, SGOT, alkaline phosphatase, urea, creatinine, total proteins) was performed, and heart rate and blood pressure were measured before and after treatment.

Compliance was evaluated by counting the medications returned unused.

Analysis

The concept of the severest symptom score was used for symptom analysis and to assess the efficacy of treatment. This method has been successfully used in previous studies (Masi et al., 1993; Jobst et al., 1994; Clement et al., 1994) as a tool to assess overall symptom relief and patient comfort. It involves the use, on a daily basis, of the score for the symptom most troublesome to the patient. The primary efficacy variable was derived from patient self-evaluation scores.

We selected each day, for every patient, the highest symptom score recorded in the patient's diary, i.e. the score of the most troublesome symptom. Highest daily scores were then used to calculate for each patient the percentage of study days when the highest score was 0 (asymptomatic days) or when the highest score was ≤1 (the percentage of days when symptoms were absent or mild, i.e. comfortable days). For nasal congestion, similar cumulative frequencies were computed to determine the percentages of study days, both without nasal congestion and when nasal congestion was absent or at most mild.

Baseline for the daily symptom scores was defined as the highest score for any of the five symptoms on day 0 (day before visit 1) and day 1 (day of visit 1), and was thus based on two pre-treatment patient evaluations. The most severe symptom scores were also computed for the scores recorded by investigators at baseline, visit 2 and visit 3. These also utilised the score of the most troublesome symptom, i.e. the highest score at each visit. Analyses were performed on all randomised patients (intention-to-treat analysis). When a baseline value was available, it was taken into account in the treatment comparison. Global tests for independent groups were first used to compare the three treatment groups. If a statistically significant difference was found, pairwise comparisons (CTZ *versus* COM, PER *versus* COM, and CTZ *versus* PER) were performed (Cochran-Mantel-Haenszel test, Fisher's exact test, Wilcoxon rank sum test).

To support this first analysis, the daily changes of the mean symptom scores in each group, for each symptom, were detailed and studied using regression analysis of repeated measures by the generalised estimating-equations approach of Liang and Zeger (1986; constant correlation between any two observation times, normal response) with the RMGEE programme (Davis, 1993).

Adverse events, whether or not related to the study medication, were classified according to the Costart terminology, and their occurrence was compared by the Pearson's chi-square test. All tests were two-tailed.

RESULTS

Two hundred and ten patients (70 in each group) included in the study were analysed for efficacy and safety. The three groups were comparable with regard to sex, age, duration of rhinitis and baseline symptoms (Table 1).

Table 1. Patient's demography.

	CTZ	PER	COM
sex			
M	32	33	32
F	38	37	38
age (years)			
X±SD	28.7±12.1	24.4±8.4	27.5±11.9
range	13-65	10-58	12-68
duration of rhinitis (years)			
X±SD	7.5±7.2	6.4±5.8	8.0±7.6
range	1-40	0-21	1-36
baselines scores (diary) max. 5-symptom score (day 0 and 1)			
X±SD	2.4±0.6	2.4±0.6	2.3±0.7
nasal congestion (days 0 and 1)			
X±SD	2.2±0.7	2.1±0.7	2.1±0.8

Efficacy: Symptom evaluation by patients

Cumulative scores indicating the percentages of asymptomatic and comfortable days are summarised in Table 2. The mean percentages of asymptomatic days were 6.8%, 5.1 % and 11.8% in the CTZ, PER and COM groups, respectively. None of these differences were statistically significant.

Table 2. Percentages of days over whole-study period when symptoms and nasal congestion were absent or mild.

	CTZ	PER	COM
percentage of asymptomatic days	6.8±16.4	5.1±11.0	11.8±22.7
percentage of comfortable days	45.5±36.4	40.6±30.6	64.8±30.1
percentage of days without nasal congestion	16.5±28.1	18.0±26.8	30.4±33.1
percentage of days when nasal congestion is absent or mild	52.7±37.4	62.0±34.1	79.0±26.1

The corresponding mean percentages for comfortable days (i.e. days when symptoms were absent or mild) were 45.5%, 40.6%, and 64.8% in the CTZ, PER, and COM groups, respectively. COM was significantly better than both CTZ (p=0.003) and PER (p=0.0001). The difference between CTZ and PER was not statistically significant (p=0.484).

The mean proportion of days without nasal congestion was significantly greater in the COM group (30.4%) compared to both CTZ (16.5%; p=0.005) and PER (18.0%; p=0.025) groups. The difference between CTZ and PER was not statistically significant (p=0.477). The same pattern was observed for the percentage of days when nasal congestion was absent or mild: 52.7%, 62.0%, and 79.0% in CTZ, PER and COM groups, respectively. The difference between CTZ and PER was not statistically significant (p=0.139). Comparisons of COM with CTZ and PER were highly significant (p=0.0001 and p=0.003, respectively). The daily changes in symptom scores for each symptom and the statistical results are summarized in Figures 1-5. All symptoms decreased significantly with time ($p < 0.00001$). COM was more effective than both CTZ and PER alone in the relief of nasal congestion. COM was also found to improve rhinorrhoea and sneezing more than PER; CTZ was more effective than PER in relieving sneezing, nasal and ocular pruritus.

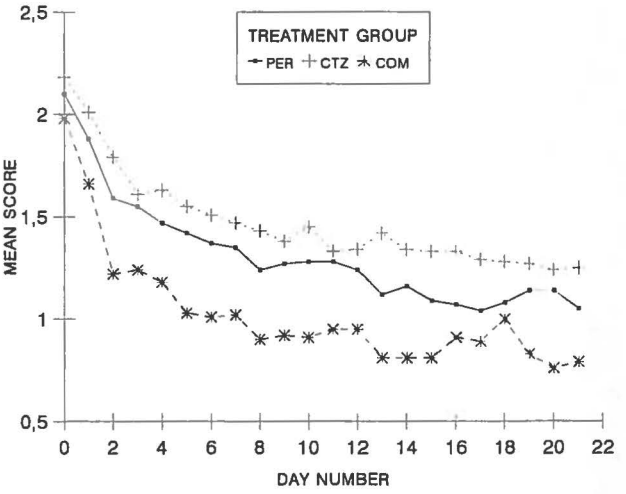

Figure 1. Nasal obstruction mean score *versus* treatment days (COM *versus* CTZ: $p<10^{-4}$; COM *versus* PER: p=0.004; CTZ *versus* PER: NS [p=0.128]).

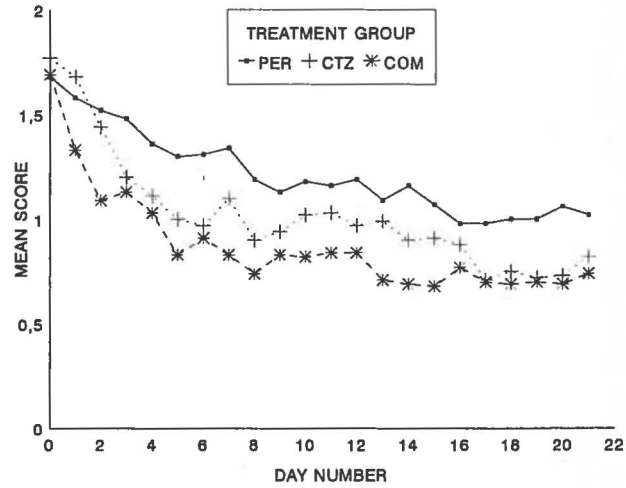

Figure 2: Rhinorrhoea mean score *versus* treatment days (COM *versus* CTZ: NS (p=0.174); COM *versus* PER: p=0.001; CTZ *versus* PER: NS [p=0.072]).

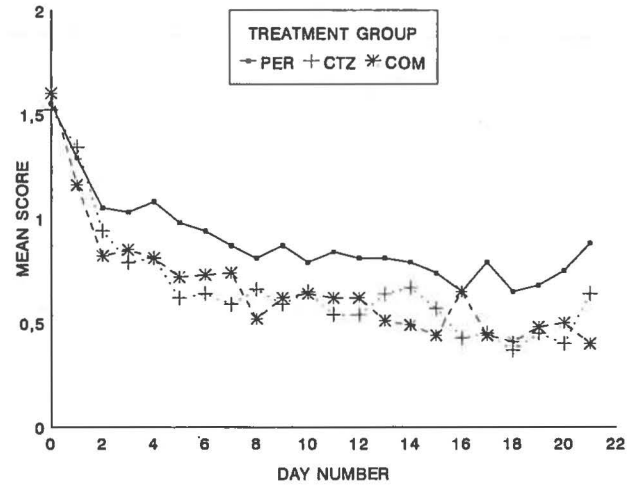

Figure 3: Sneezing mean score *versus* treatment days (COM *versus* CTZ: NS (p=0.790); COM *versus* PER: p=0.021; CTZ *versus* PER: p=0.012).

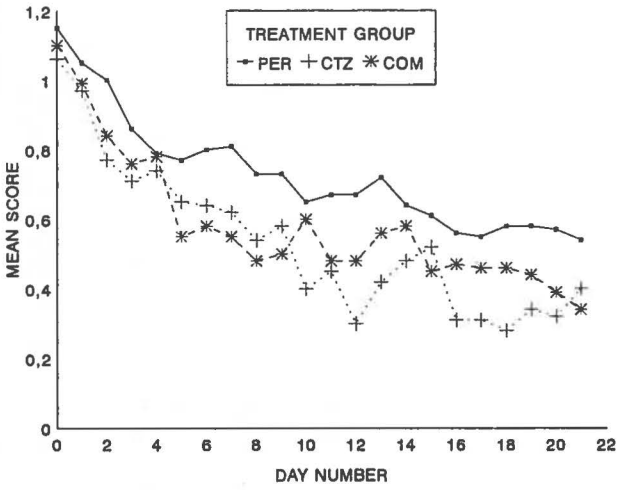

Figure 4: Nasal itching mean score *versus* treatment days (COM *versus* CTZ: NS (p=0.384); COM *versus* PER: NS (p=0.158); CTZ *versus* PER: p=0.018).

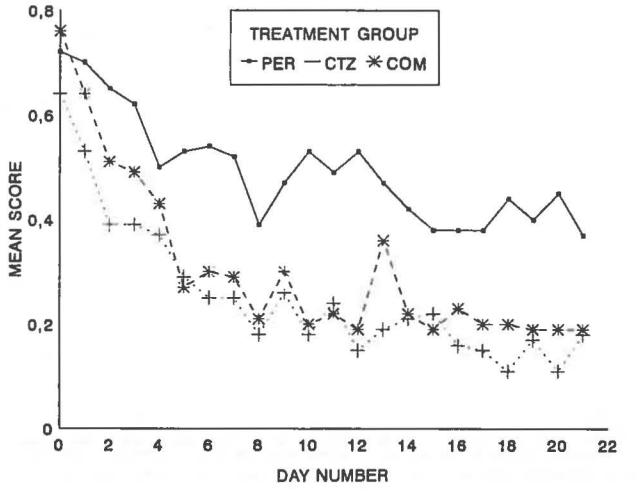

Figure 5: Eye itching mean score *versus* treatment days (COM *versus* CTZ: NS (p=0.204); COM *versus* PER: NS (p=0.080); CTZ *versus* PER: p=0.006).

Efficacy: Symptom evaluation by investigators

The most severe symptom scores of the three treatment groups were comparable at baseline (visit 1). Scores in all groups improved at visit 2 and improved still further at visit 3. At the second visit, COM (mean score: 1.38) improved more than both CTZ (mean score: 1.76) and PER (mean score: 1.85; p=0.001, for both comparisons). At the third visit, however, we found no statistical differences between the three treatments.

Global evaluation by investigators at the end of treatment was also in favour of COM compared to both CTZ (p=0.028) and PER (p=0.018) with responses considered excellent or good in 66%, 53%, and 42% in COM, CTZ and PER groups, respectively (Table 3).

Table 3. Global evaluation of treatment.

	CTZ n (%)	PER n (%)	CO n (%)
worse	0	3 (4.6)	0
no change	15 (21.4)	9 (13.6)	9 (13.4)
slight improvement	18 (25.7)	26 (39.4)	14 (20.9)
marked improvement	33 (47.1)	20 (30.3)	31 (46.3)
excellent improvement	4 (5.7)	8 (12.1)	13 (19.4)
total	70	66	67
data missing	0	4	3

Combination *versus* cetirizine: p = 0.028; combination *versus* pseudoephedrine: p = 0.018

Safety

Although the total incidence of adverse events was highest in the PER group, the differences between groups were not statistically significant (Table 4).

The most frequently reported adverse events in the CTZ group were somnolence (8.6%) and bronchitis (5.7%). In the PER group, insomnia was most frequently reported (10%); other adverse events were dry mouth and nausea (both 8.6%), headache (7.1%), and asthenia (5.7%). One instance of hallucinations was reported as a serious event.

In the COM group, somnolence was most frequently reported (12.9%), followed by headache (11.4%), pharyngitis (7.1%), and dry mouth, asthenia, insomnia, nervousness and rhinitis (each 5.7%). No clinically relevant change was observed in laboratory tests, heart rate or blood pressure at the end of the treatment.

Table 4. Adverse events*.

	CTZ n = 70	PER n = 70	COM n = 70
number of patients who reported any adverse events	31	38	35
costart term			
asthenia	2	4	4
headache	3	5	8
dry mouth	0	6	4
nausea	0	6	0
insomnia	1	7	4
nervousness	1	1	4
somnolence	6	3	9
bronchitis	4	0	0

* All reported adverse events whether or not considered to be related to treatment.

Study withdrawals

Seven patients in the CTZ group, 19 in the PER group, and 13 in COM group withdrew from the study (Table 5).

Table 5. Study withdrawals.

	CTZ n = 70	PER n = 70	COM n = 70
inefficacy	1	2	0
adverse event	2	9	4
protocol violation or personal reasons	4	8	9

DISCUSSION

We have shown, from patients' self-evaluation of symptoms, that combined treatment with cetirizine and pseudoephedrine produced better relief of symptoms of perennial allergic rhinitis than either cetirizine or pseudoephedrine given as single agents. This finding is supported by the results of symptom evaluation by investigators and their global assessment at the end of the study. Symptom evaluation, based on daily scoring by patients, and at each visit by investigators, of the most troublesome symptom present proved to be a sensitive method of analysis. We compared treatment groups with regard to the proportion of study time when symptoms of rhinitis were under sufficient control, i.e. days when patients were either symptom-free or complained at most of mild symptoms. This approach, which has been previously shown to be sensitive (Masi et al., 1993; Jobst et al., 1994; Clement et al., 1994), allows a reliable assessment of outcome without the need for multiple timepoint comparisons throughout the day. Symptoms expressed as symptom-free and comfortable days also reflect quality of life, in that they do not disturb either daily activities or sleep.

Other commonly reported methods of analysis, such as mean and total symptom scores do not reflect the concept of comfort in performing daily activities, because the degree of a patient's discomfort is governed more by symptom severity than the nature of the symptom. Thus, a truck driver may be highly disturbed by excessive sneezing, while the main source of discomfort to a radio announcer may be nasal obstruction. A more conventional approach was adopted by analysing the course of each symptom during the 3-week treatment period (Figures 1–5).

Combination therapy was more effective than both single agents in relieving nasal obstruction, indicating an additive effect of each drug. This perhaps suggests that cetirizine and pseudoephedrine may act at different sites (Svensson et al., 1992). That combination treatment was more effective than pseudoephedrine, but not cetirizine, in the relief of sneezing and rhinorrhoea is not surprising because these symptoms are mainly histamine-induced and therefore likely to be relieved by a H_1-antagonist (Simons, 1989; Naclerio, 1991). There was no significant difference between the three treatment groups in the relief of nasal and ocular pruritus and this might have been due to the mild nature of these symptoms at baseline.

A clinical rationale for combination therapy exists only if the combination can be shown to possess enhanced efficacy compared to each single agent without an increase in adverse events. We have shown clinical benefit in this study, in that the combination of cetirizine and pseudoephedrine provided better symptom relief and patient comfort than either cetirizine or pseudoephedrine alone. More rapid and more marked relief of discomfort was seen when nasal obstruction was present. To the best of our knowledge, this therapeutic effect has not been previously been clearly shown in perennial allergic rhinitis. Although positive effects on nasal provocation tests with allergies have been reported with a terfenadine and pseudoephedrine combination, these have not been confirmed clinically with statistical proof (Henauer et al., 1991).

Adverse events observed for cetirizine and pseudoephedrine in this study are consistent with published reports (Dickerson et al., 1987; Spencer et al., 1993). Tolerance was best in the cetirizine group (with fewer and less severe adverse effects), but this was not a clinically relevant advantage over the combination because of the increased efficacy of the latter. No clinically significant abnormalities were found.

In conclusion, the cetirizine (5 mg) and pseudoephedrine (120 mg) combination taken twice a day is well tolerated and more effective than each agent taken separately for the control of symptoms of perennial allergic rhinitis, especially when nasal congestion is the predominant symptom.

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B. Bertrand, MD
ENT Department
Cliniques Universitaires UCL de Mont-Godinne
Avenue Therasse 1
B-5530 Yvoir
Belgium