The Journal of Laryngology and Otology
November 1998, Vol. **112,** pp. 1042–1046

The effect of cetirizine on symptoms and signs of nasal polyposis

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Abstract

Forty-five patients with residual or recurrent nasal polyposis after ethmoidectomy were treated with either cetirizine at twice the daily recommended (20 mg) dose or placebo for three months. The number and size of polyps remained unchanged during the study period. Cetirizine was found to reduce nasal sneezing and rhinorrhoea effectively. The drug also had a beneficial effect on nasal obstruction in the latter part of the study. The side effects of 20 mg (double the recommended daily adult dose) of cetirizine were few and comparable to placebo.

Key words: Nasal polyps; Histamine H_1 receptor blockaders

Introduction

Nasal polyposis is an inflammatory disease, affecting particularly the ethmoidal sinuses and results in nasal obstruction (Drake-Lee, 1994). Many patients also suffer from high levels of rhinorrhoea and in addition, some have sneezing which can be troublesome (Drake-Lee *et al.*, 1984). The aetiology of the condition is unknown but eosinophilia is a marked histopathological finding (Jahnsen *et al.*, 1995).

Cetirizine, a second generation histamine H_1-antagonist, is indicated for the treatment of allergic rhinitis and urticaria. It has significantly fewer side effects than the older first generation compounds, for example, on the central nervous system. In addition, cetirizine has other properties that are under investigation. In the *in vivo* skin chamber and blister technique it has been shown to inhibit infiltration of eosinophils into the allergen-challenged sensitive skin (Fadel *et al.*, 1987; Charlesworth *et al.*, 1989). Such inhibition has also been seen after conjunctival provocation (Bagnasco and Canonica, 1995) and in nasal epithelia in mite allergy (Ciprandi *et al.*, 1995; Fasce *et al.*, 1996).

Thus, cetirizine might have an important influence on the pathological manifestations of diseases with marked eosinophilia such as nasal polyposis. This study was therefore undertaken to investigate the effects of cetirizine on this condition.

Materials and methods

In this double-blind study, 45 adult patients with bilateral nasal polyposis for at least two years, who had undergone ethmoidectomy and were left with small residual or recurrent polyps, were investigated by two otolaryngologists using identical methodology through randomization in blocks of four. Twenty-three of the patients received 20 mg cetirizine once daily and 22 received placebo tablets of identical appearance for three months.

The principal inclusion criteria were: nasal polyps demonstrable on rigid nasal endoscopy, nasal eosinophilia as documented from nasal secretions or biopsy, age between 18 and 68 years and a history of having undergone nasal polypectomy between two months and two years prior to the commencement of the study. Symptoms had to be present for at least two years with nasal blockage as the most prominent clinical symptom. The main exclusion criteria were: nasal structural abnormality, unilateral nasal symptomatology, history of intolerance to acetylsalicylic acid (aspirin), diabetes mellitus, hypertension and purulent nasal discharge with or without neutrophilia. The use of systemic corticosteroids, histamine H_1-antagonists, antihypertensives, psychosedatives or topical vasoconstrictors within the preceding four weeks (including run-in period) (astemizole six weeks) and during the study was also prohibited. The maximum permitted daily dose of inhaled bronchial corticosteroids was set at less than or equal to 800 μg.

In order to counteract the possible confounding factor of pollen-induced allergic rhinitis, patients with this condition were studied outside of the pollen season.

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Accepted for publication: 9 July 1998.

Patients were required to fill in a daily diary card grading the following symptoms: nasal obstruction, rhinorrhoea and sneezing on a scale ranging from zero to three: (0: no discomfort – 3: severe discomfort). All additional medication not specifically prohibited under 'exclusion criteria' was recorded on a daily basis by the patient.

Following the two week run-in period, each patient was reviewed by the same investigator both at study commencement and every four weeks thereafter for a period of up to three months. At each review visit, rigid nasal endoscopy was performed. The number of nasal polyps was recorded and the diameter of the largest polyps was measured and scored according the following scale:

(1) ≤3 mm
(2) >3 mm and ≤6 mm
(3) >6 mm and ≤9 mm
(4) >9 mm

In addition, nasal symptoms as defined above and adverse effects were recorded.

Data were analysed on an intention-to-treat basis, so all patients randomized to treatment groups were included in the analysis. All tests were two-tailed and were performed at the five per cent level of significance. Group comparability was accepted for p-values above 0.10. All statistical tests were non-parametric: Mann-Whitney U-test to compare quantitative data and chi-square to compare qualitative data.

Results

The mean age and standard deviation in each patient group were: cetirizine : 45 ± 12 years, placebo: 45 ± 9 years (p = n.s.). The genders of the patients were comparable (Table I). Amongst these, 13 patients (cetirizine: 6; placebo: 7) had concomitant asthma and 16 (cetirizine: 8; placebo: 8) had documented allergies. Of the eight patients who inhaled bronchial steroids, none used more than 400 μg daily. Of the 45 patients enrolled, 36 completed the study, 18 from each group; the causes for withdrawal are summarized in Table II.

The duration of nasal obstruction was 12 ± 8 (mean ± standard deviation) years. Visible nasal polyps had been present for 7 ± 6 (mean ± standard deviation) years in all patients. No difference was observed between the groups.

The evolution of the global symptom score as noted by the investigator is shown in Figure 1. No significant differences were found between treatments. However, when considering the daily diary card as filled in by the patient, cetirizine had a statistically significant effect on each symptom (Figure 2). With regard to rhinorrhoea, the percentage of days with no or only mild symptoms was significantly higher under cetirizine throughout the entire study. As regards sneezing, with the exception of the final measurement after 12 weeks of treatment, a similar pattern was noted. Nasal obstruction significantly improved under cetirizine at the end of the study. This latter improvement is also illustrated in Figure 3.

No change in the size and number of polyps occurred in either treatment group throughout the study.

No withdrawals occurred in the first four weeks of the study. Nine patients withdrew subsequent to this time: within this number, two in each group had recurrent polyp growth and required additional therapy. Additional withdrawals were due to adverse events, namely infection or somnolence. All cases were equally distributed between the two treatment groups (Table II).

Twenty-eight patients reported adverse events throughout the entire study, with a balanced distribution between the two groups (cetirizine: 14; placebo: 14). Of these, two from each group were regarded as drug-related (somnolence). Six patients, three from each group, reported headache and in one patient (cetirizine), the relationship to the study drug was reported as possible.

TABLE I
GENDER

	Active	Placebo	Total
	N	N	N
Male	18 (78%)	17 (77%)	35 (78%)
Female	5 (22%)	5 (23%)	10 (22%)
Total	23 (51%)	22 (49%)	45 (100%)

TABLE II
CAUSES FOR WITHDRAWAL N = 9

	Cetirizine	Placebo
Polyp regrowth	2	2
Infection	2	1
Somnolence	1	1
Total	5	4

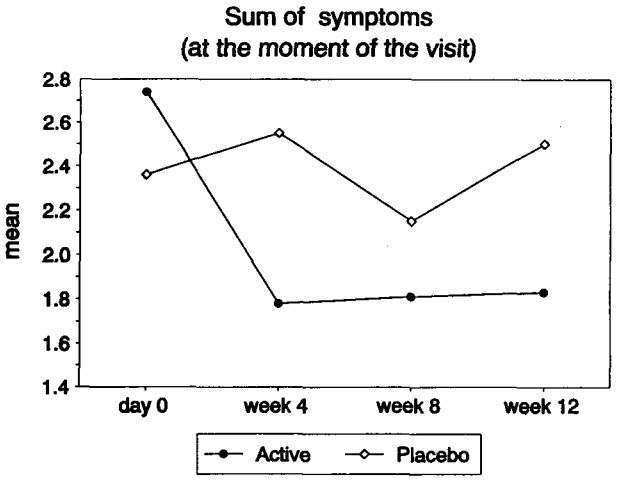

FIG. 1
Sum of symptoms (at the moment of the visit)

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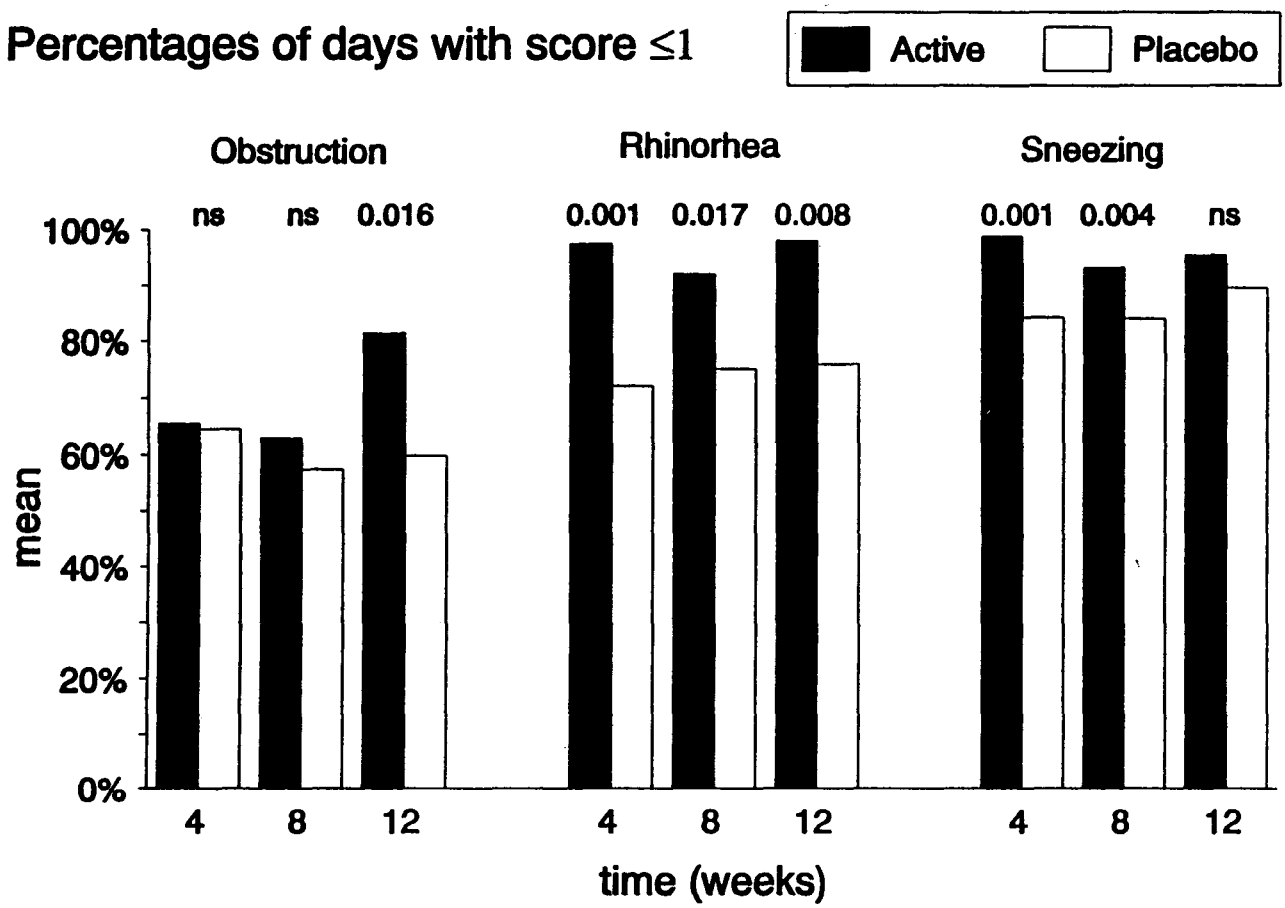

FIG. 2
Percentages of days with score ≤1

Discussion

Patients with nasal polyposis constitute a heterogeneous group. For this reason, it was decided to investigate only patients with the lowest recurrence rate, eg. not those with cystic fibrosis and acetylsalicylic acid (ASA) intolerance. The study group was also confined to those with bilateral polyps who had tried topical steroids unsuccessfully and who had opted for ethmoidectomy instead of a course of systemic steroids as an alternative (Lildholdt *et al.*, 1988). In order to evaluate the effect of treatment, only those patients who had residual or recurrent small polyps that could be measured and counted were enrolled.

Forty-five patients were accordingly enrolled and equally randomized to receive either cetirizine or placebo. The mean age of 45 years is comparable to that obtained in other studies (Moloney, 1977; Drake-Lee *et al.*, 1984) as is the male preponderance of patients. The study can therefore be considered to be representative of the condition of nasal polyposis.

All polyps were easy to count and measure. The product of polyp number and size from both nasal cavities were comparable between the two groups and no differences were noticeable for this parameter for the entire study period. Thus, cetirizine appears to have no influence on the growth of polyps either positively or negatively. Changes in the nasal mucosa were difficult to detect; anterior rigid endoscopy may not be the ideal method. Acoustic rhinometry might be more appropriate in order to quantify changes in nasal patency, particularly at the level of the inferior concha (nasal valve). Changes in the size of polyps in the nasal cavity can also be measured by the latter method, but not in the intraethmoidal region.

The mean combined symptom score improved in the cetirizine-treated group compared to placebo, but this improvement did not attain statistical significance. However, the patients' diary cards, gave more detailed information of changes in the symptoms, since they were recorded on a daily basis. From the start there was a significant and beneficial effect of cetirizine on rhinorrhoea, which can be troublesome in nasal polyposis (Drake-Lee *et al.*, 1984; van Camp *et al.*, 1994). Although allergy is not deemed to be an important cause of nasal polyposis (Slavin, 1992), an increased number of mast cells (Cauna *et al.*, 1972) and histamine content (Bumstead *et al.*, 1979) has been found in the polyps when compared to normal mucosa. Therefore, the antihistaminic property of the drug is important, but other non-histamine H_1 receptor mechanisms cannot be ruled out.

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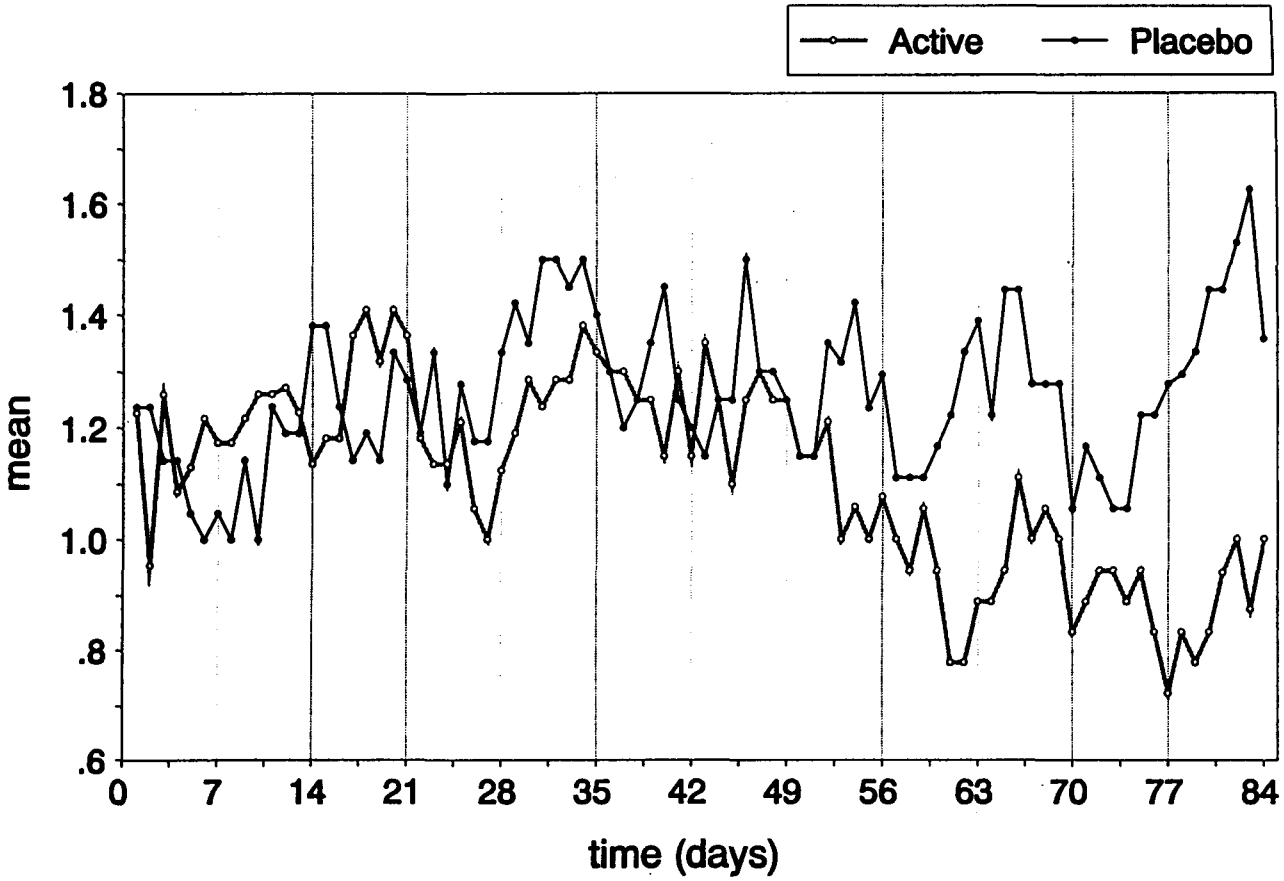

FIG. 3
Nasal obstruction (daily cards)

Sneezing was not as frequent as reported elsewhere (Drake-Lee *et al.*, 1984) but nevertheless, cetirizine reduced this symptom also.

Although we could not observe any changes in the number of size of polyps between the groups, the patients' diary cards showed a significant decrease in nasal obstruction in the cetirizine-treated group in the last month of the study. This may be due to non-antihistaminic properties of cetirizine directly influencing the pathology of the nasal mucous membrane via an inhibitory effect on ICAM-1 expression, thus creating a better patency (Ciprandi *et al.*, 1995; Haye *et al.*, 1995; Fasce *et al.*, 1996).

In this three-month-long study with cetirizine used at twice the recommended adult daily dose, 28 patients reported 39 adverse events; these were evenly distributed between the two treatment groups. Of these, four events (somnolence: placebo = 2, cetirizine = 1, increased appetite: cetirizine = 1) were reported as very likely to be drug-related. In this way, cetirizine was seen to be well-tolerated in this long-duration high-dose study.

In conclusion, although it does not influence the size of the polyps, cetirizine has a definite place in the treatment of symptoms associated with nasal polyposis and is safe to use.

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