

Short communication

Cetirizine treatment of allergic cough in children with pollen allergy

Ciprandi G, Tosca M, Ricca V, Passalacqua G, Fregonese L, Fasce L, Canonica GW. Cetirizine treatment of allergic cough in children with pollen allergy.

Allergy 1997; 52: 752–754. © Munksgaard 1997.

Cetirizine, an antihistamine widely used in the treatment of allergic rhinoconjunctivitis, also has antiallergic activity. The present study aimed to evaluate cetirizine as a treatment for children with allergic cough due to pollen allergy. This was a parallel-group, double-blind, placebo-controlled, randomized study. Twenty children with pollinosis were enrolled: they were subdivided into two groups receiving a 1-month treatment during the pollen season. The following variables were monitored: 1) clinical symptoms and respiratory data (spirometry and PEF) evaluated at baseline and at the end of the study by allergists and by a daily diary card, and 2) pollen count. This study shows that cetirizine treatment reduces cough intensity ($P < 0.05$) and frequency ($P < 0.01$). In conclusion, cetirizine does clinically improve cough due to pollen allergy.

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Key words: allergic cough; antihistamines; cetirizine; pollen allergy.

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Accepted for publication 3 February 1997

Cough is often a concomitant symptom of allergic rhinoconjunctivitis and asthma (1, 2). A history of cough strictly associated with allergic rhinoconjunctivitis, occurring during natural allergen exposure, strongly supports an allergic immunologic inflammatory origin of this cough, although other factors cannot be ruled out.

On the other hand, our knowledge of the cause and pathophysiology of allergic asthma and asthma equivalents, including cough, has progressed immensely, as has the spectrum of therapeutic agents and delivery systems presently available to treat these conditions (3–5). In this regard, the role of antihistamines has recently been reconsidered prospectively for several reasons (6–8). Newer antihistamines show, both in *in vitro* and in *in vivo* models, additional antiallergic properties that might help to reduce the early- and the late-phase allergic reaction (9). The relatively high antihistaminic concentration able to produce a therapeutic effect on bronchoconstriction can be obtained with the new highly selective H_1 -receptor antagonists, which are devoid of sedative effects (9).

We previously studied the effectiveness of terfenadine in the treatment of allergic cough in children

in an open pilot study. We demonstrated a reduction of clinical severity and frequency of cough in young patients treated with terfenadine (10). More recently, in a controlled study, we demonstrated that loratadine reduces cough intensity and frequency in adult patients with pollen allergy (11).

Cetirizine, a carboxylated metabolite of hydroxyzine, is a highly-selective antihistamine, with additional antiallergic effect since it prevents changes consequent to allergen-specific challenges and reduces eosinophil and neutrophil infiltration to the site of allergic reaction (12). The present study was designed to assess the possible effectiveness of cetirizine in the management of cough associated with allergic rhinoconjunctivitis in children with pollen allergy, considering clinical and inflammatory factors.

Material and methods

In a double-blind, placebo-controlled, parallel-group, randomized study, 20 patients (nine boys and 11 girls) 6–15 years of age (mean 8.5 years), with cough associated with allergic rhinoconjunctivitis, were enrolled and studied during the pollen

season. The patients had a history of cough associated with allergic rhinoconjunctivitis due to *Parietaria judaica* and/or grass pollen for at least two previous seasons, without clinical asthma, positive skin prick test, and RAST for the specific pollen(s). None of the patients were sensitized to other allergens, and they were symptom-free outside the pollen season. They had no other ocular and nasal diseases. The absence of any concomitant pulmonary function alteration related to asthma (also mild) and of irreversible bronchostenosis was carefully checked at baseline: all patients had more than 80% of predicted forced expiratory volume in 1 s (FEV₁). Patients with a history of asthma were excluded, as were patients with previously documented intolerance of the studied drug. Allergic subjects had not received topical or systemic drugs in the preceding 6 weeks, nor specific immunotherapy before and during the study. All the subjects' parents gave their informed consent, and the trial was approved by the department ethics committee.

Patients received either cetirizine 0.15 mg/kg body weight daily in the morning or placebo for 4 weeks. Occurrences (as frequency and severity) of cough attacks were assessed four times daily, according to a questionnaire previously completed (10, 11) by each patient's parents. Cough symptoms were graded according to a four-point rating scale: 0 = absent, 1 = mild, 2 = moderate, and 3 = severe. The scale was also explained and discussed with the parents, as in previous studies (10, 11). Peak expiratory flow (PEF) evaluation was performed twice a day, i.e., morning and evening, and reported in a diary card. Each PEF recording involves choosing the best of three performances.

Measurements of pulmonary function were made with a bell spirometer (SensorMedics Corporation, Yorba Linda, CA, USA). Any adverse event emerging during the study and spontaneously reported by the patient was carefully evaluated and monitored. An overall judgment of the efficacy and safety of the treatment was expressed by both investigator and patient at the end point.

For statistical analysis, Friedman's ANOVA test and the Mann-Whitney test were used.

Results

The two studied groups were homogeneous at baseline for all the considered variables. All patients completed the study. All of them showed signs and symptoms of allergic rhinoconjunctivitis and cough at the beginning of the study.

The cetirizine-treated group showed a significant clinical improvement of weekly cough intensity and frequency during the treatment (Fig. 1). Cetirizine

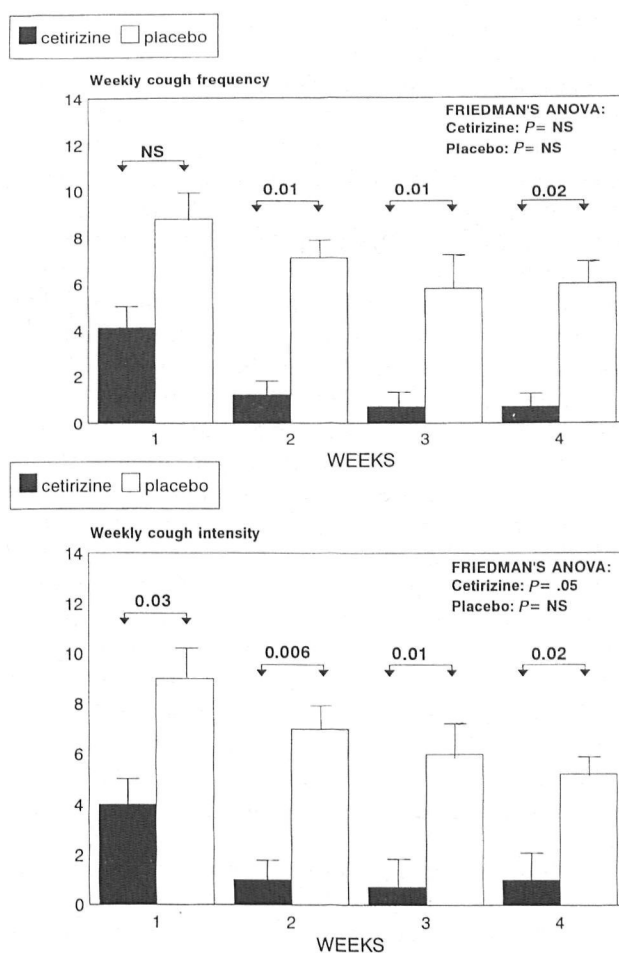


Fig. 1. Mean cough frequency (upper) and cough intensity (lower) week per week in treated and placebo groups. Intergroup-comparison P values are reported on bars.

decreased the cough frequency from week 2 of treatment ($P < 0.01$) and in the following weeks (Fig. 1). Cetirizine reduced cough intensity more than placebo from week 1 of treatment ($P = 0.03$) and in the following weeks (Fig. 1). No change in PEF and FEV₁ values was observed during the study period. Cetirizine's overall therapeutic effectiveness was judged satisfactory in all patients, including nasal and ocular symptoms (data not shown). Cetirizine's safety was generally perceived as excellent by both the patients' parents and the investigators, since no significant adverse events were reported by patients during the treatment period.

Discussion

The clinical effectiveness and therapeutic value of antihistamines in the treatment of allergic diseases have been extensively demonstrated (9, 10). The older antihistamines have not been favored for the clinical management of bronchial asthma because

of their unsatisfactory efficacy at the recommended dose, and they have unacceptable anticholinergic, antiserotonin, α -adrenergic antagonist effects and sedative side-effects at considerably higher doses (13). The currently available newer antihistamines have recently been re-evaluated in the treatment of bronchial asthma (7–10). Several clinical studies have demonstrated the therapeutic usefulness of antihistamines in mild allergic asthma and cough, and this has been supported by pharmacologic evidence of a protective role of antihistamines in specific and nonspecific challenge tests (7–10). These newer H_1 -receptor antagonists are characterized by high H_1 -receptor selectivity, antiallergic properties, favorable kinetics, and minimal sedative effects (7, 9). They have greatly contributed to our understanding of histamine's role in asthma and of antihistamine use in asthma treatment (7, 9). Thus, antihistamines may be effective in the clinical management of cough associated with allergic rhinitis due to pollen, which may be the sole manifestation of allergic asthma (1). In this regard, we have recently demonstrated terfenadine's clinical efficacy in the treatment of allergic cough in children (11), and loratadine's effectiveness in adults with allergic cough due to pollen allergy (12).

Cetirizine is a new antihistamine with bronchodilator activity (14) and antiallergic properties (12). In the present study, all cetirizine-treated patients showed a reduction of the frequency and intensity of cough.

A first possible mechanism of action of cetirizine may derive from its antihistaminic activity: in fact, histamine induces, at least partly, bronchial irritation through H_1 receptors (1).

However, allergic cough is sustained by other, different pathogenic mechanisms: other mediators (such as leukotrienes, prostaglandin, and platelet-activating factor) and overall airway inflammation.

Although several factors can trigger airway inflammation, in the case of cough associated with allergic rhinoconjunctivitis, the immunologic inflammatory origin of this condition is strongly indicated. According to the current literature, allergic cough may be regarded as a variant type of asthma that may progress to clinical asthma (1, 2) when, for instance, allergen exposure is high. Current knowledge of the pathophysiology of allergic inflammation includes the presence of eosinophil influx and activation. Eosinophils are the main cause of epithelium desquamation since they release basic proteins (such as eosinophil cationic protein, major basic protein, and eosinophil protein X) able to damage epithelial cells. Recently, epithelial damage

due to eosinophilic infiltration has been related to an increased cough response (1), as, in fact, denudation of sensory nerve endings (cough receptors) may result in an increased cough response to exogenous or endogenous factors. The possible mechanisms of action of cetirizine on allergic inflammation (such as eosinophil infiltration at mucosal level and its activation) may be due to different effects on eosinophil functions, concerning both activation (i.e., metabolic activities and release of mediators) and migration from the bloodstream into the mucosa (12).

The results of the study support the use of cetirizine in the treatment of allergic cough. Since previous studies have shown the effectiveness of their action on cough of some of the new generation of antihistamines (7–10, 12, 13), which act on the inflammatory events of allergy, these drugs appear to be useful tools in the clinical control of allergic cough.

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