

The use of anti-H₁ drugs in mild asthma

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Antihistamines have been used in the treatment of allergic rhinitis and urticaria for many years. However, conventionally, they have not been prescribed for asthma (1). The purpose of this paper is to reexamine the appropriateness of this judgment.

Exposure of a sensitized subject to an allergen results in the release of histamine which can affect the airways, causing bronchospasm, an increase in secretions, and edema. Histamine has long been considered to be a major mediator of the allergic reaction, particularly with regard to the early-phase reaction, and histamine-releasing factors are thought to play a role during the late-phase reaction. Numerous lines of evidence support the view that histamine is important in the pathogenesis of asthma. Histamine is present in the sputum and bronchoalveolar lavage (BAL) fluid of atopic asthmatic patients after antigen challenge, and its metabolite, methyl histamine, can be recovered from the urine after an antigen- or exercise-induced asthmatic attack. Inhalation of histamine produces dose-dependent bronchial constriction which is greater in asthmatic patients than in normal subjects.

Many asthmatic patients show an enhanced ability to release histamine spontaneously, as compared with normal subjects. Patients receiving medication release less histamine than those not receiving treatment (2) (Fig. 1). The level of histamine in the BAL from allergic asthmatic patients is higher than that from allergic rhinitic patients or normal subjects. Casale et al. (3) did segmental antigen challenge in normal subjects and asthmatic patients, and found increased histamine levels and increased bronchoconstriction in the challenged segmental area in the asthmatic group. Children with acute asthma have higher than normal levels of plasma histamine, which drop after therapy. Moreover, in this study, the patients with more severe disease also had higher levels of plasma histamine (4). Casale et al. (5) also showed that increased levels of histamine in the BAL were associated with increased hyperresponsiveness as judged by methacholine challenge. Patients with higher

levels of histamine required less methacholine to cause a significant rise in airway obstruction. In summary, histamine is present in the upper and lower airways and can be released spontaneously and also by stimuli such as antigen. Furthermore, it can contribute to the bronchial hyperreactivity seen in asthmatic patients (6).

Why, then, are antihistamines not more widely used for asthma treatment and in some instances actually avoided (7)? One reason is the widely held, but largely unsubstantiated, belief that the well-

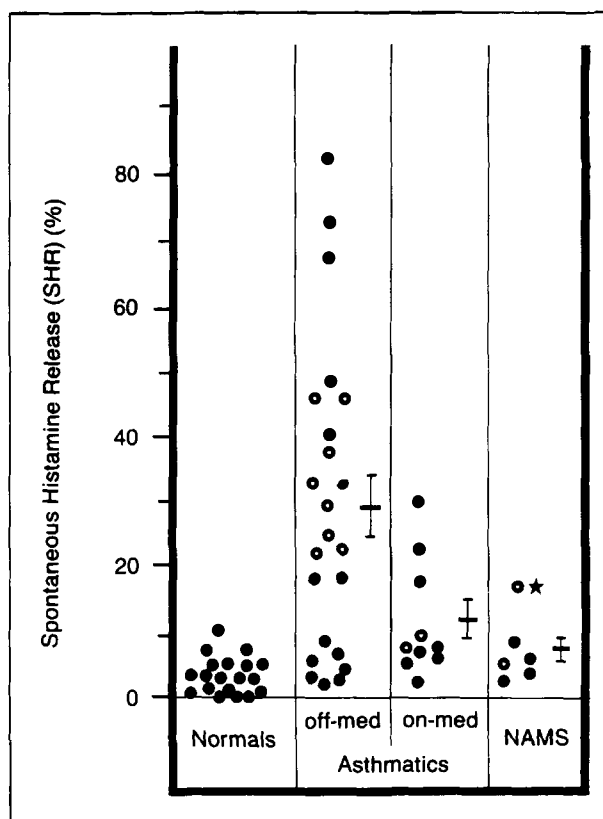


Fig. 1. Spontaneous histamine release from basophils of normal subjects compared with that of subjects with asthma not receiving and receiving medication, and nonasthmatic allergic rhinitis subjects (NAMS). With permission, Akagi K & Townley RG (2).

documented anticholinergic effects of the older antihistamines dry secretions, thereby making asthma worse. Moreover, the sedative effects of the older preparations limit the doses that can be tolerated and may in part explain the poor results of clinical studies (8). There is little evidence that antihistamines cause bronchoconstriction; indeed, their bronchodilating effects have been demonstrated (7, 9). Nonetheless, many antihistamines carry warnings on their packaging advising against their use by asthmatic patients. However, after reviewing the issues, the American Academy of Allergy and Clinical Immunology prepared the following position statement: "Antihistamines are not contraindicated in patients with asthma unless an adverse reaction has been previously demonstrated" (10).

The second-generation antihistamines have distinct advantages over the older drugs in terms of specificity and safety. Various clinical trials have been performed with these drugs to assess their safety and efficacy in the treatment of mild asthma. A selection of these will be reviewed.

Wood-Baker & Holgate (11) compared the bron-

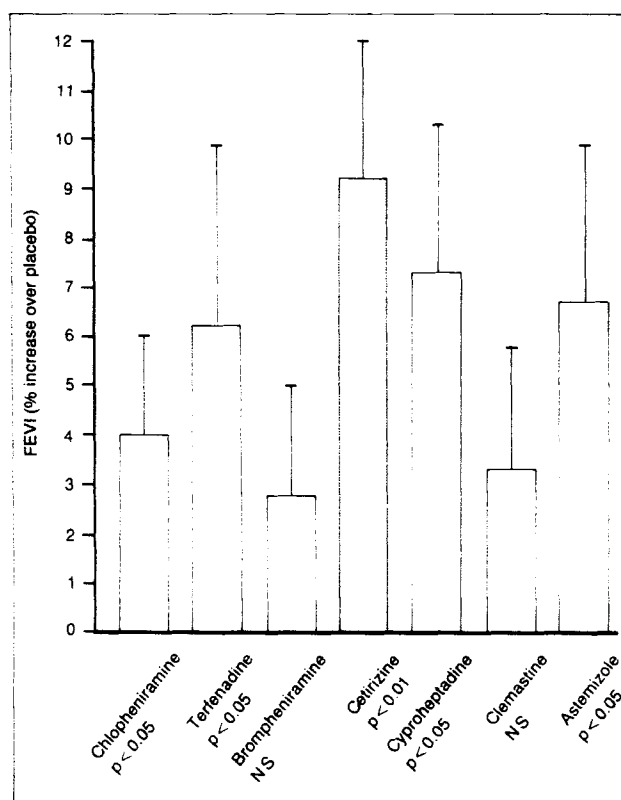


Fig. 2. Bronchodilator action of H_1 antihistamines expressed as percent increase in base-line FEV_1 after administration of active drug compared with that after administration of placebo. Each bar represents mean $\pm$ SEM for 18 subjects. With permission, Wood-Baker & Holgate (11).

chodilator response and inhibition of bronchospasm caused by histamine or methacholine of chlorpheniramine, terfenadine, brompheniramine, cetirizine, cyproheptadine, clemastine, astemizole, and placebo in a group of patients with asthma. All the antihistamines except brompheniramine and clemastine yielded statistically significant improvement from base line of forced expiratory volume in 1 s (FEV_1) (Fig. 2). Bronchodilators were withheld for 8 h before the study, while inhaled corticosteroid treatment was continued at the usual dose, which remained constant throughout the study period. As compared with placebo, all the antihistamines provided significant protection against histamine-induced bronchoconstriction as determined by the histamine concentration required to cause a 20% fall in FEV_1 . Cetirizine had the greatest protective effect of the antihistamines, followed by terfenadine. In contrast, none of the antihistamines had a protective effect against the bronchoconstrictor effects of methacholine (Fig. 3). Cetirizine, terfenadine, and astemizole were all well tolerated, with adverse effects not exceeding those seen for placebo. In another study, as compared with placebo, cetirizine (5, 10, and 20 mg) gave statistically significant protection against histamine-induced bronchoconstriction in a dose-dependent manner. Hydroxyzine also had a protective effect, but this was less than that observed for the 10- and 20-mg doses of cetirizine (Fig. 4). Both drugs induced significant bronchodilation (12).

Inhalation of platelet-activating factor (PAF) induces an acute, reversible bronchoconstriction greater than that seen after histamine or leukotriene inhalation. A study with mildly asthmatic

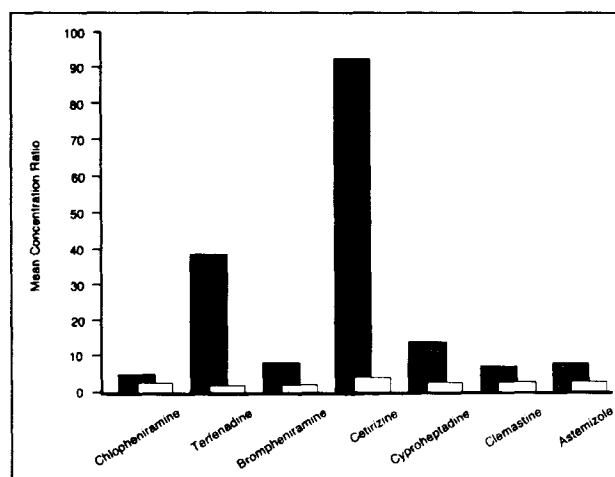


Fig. 3. Protective efficacy of antihistamines against airway response to histamine (shaded bars) and methacholine (open bars) expressed as mean concentration ratio for nine subjects who completed protocol for each inhalation challenge. With permission, Wood-Baker & Holgate (11).

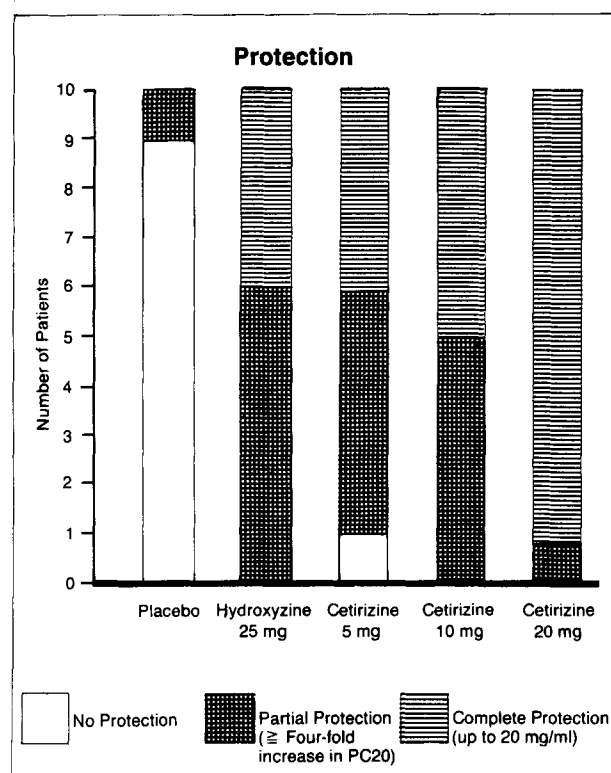


Fig. 4. Number of subjects showing complete, partial, and no protection against histamine bronchoprovocation after pretreatment with each study agent. With permission, Tashkin et al. (12).

subjects investigated the effect of cetirizine on PAF-induced bronchoconstriction. The study assessed 10 subjects in a double-blind, placebo-controlled, crossover design. Airway responses were measured by specific airway conductance (sGaw). The patients were challenged with a dose of PAF previously titrated to give a 35% fall in sGaw. PAF challenges were done after a single 15-mg dose of cetirizine and after 1-week treatment (15 mg twice daily). There was no significant effect of cetirizine on PAF-induced bronchoconstriction, nor did it modify the PAF-induced facial flushing and feeling of warmth in these patients (13).

The mode of delivery of a drug may affect its efficacy. Rafferty et al. looked at both oral and inhaled cetirizine on allergen-induced early bronchoconstriction in a double-blind, randomized, placebo-controlled trial. These workers were unable to detect a significant protective effect by either inhaled or orally administered cetirizine (14).

A similar study showed a tendency for cetirizine to protect against the allergen-induced immediate asthmatic response. These results were not statistically significant, in part because of wide individual responses to the protective effect of cetirizine, and also because of the small number of subjects enrolled (15).

The late-reaction seen some hours after allergen inhalation is thought to mimic the inflammatory situation seen in day-to-day ongoing asthma. Wasserfallen et al. (16) looked at the effect of cetirizine in the late- as well as the early-phase bronchoconstrictive reaction to allergen challenge. Once again, cetirizine had no effect on the early reaction to antigen. However, all features of the late allergic reaction, including the fall in FEV₁, were significantly improved by cetirizine (15 mg twice daily) compared to placebo (Fig. 5).

The influx of inflammatory cells is one of the hallmarks of allergic disease. This can be seen in the skin as well as in the respiratory mucosa. In atopic patients, eosinophils and other cells are attracted by intradermal injection of allergen or compound 48/80. The skin-window or chamber method allows enumeration and identification of the accumulating cells. Fadel et al. (17) used this method to show inhibition of eosinophil accumulation by cetirizine at skin sites challenged with pollen or 48/80, and these results were confirmed in a double-blind, placebo-controlled, crossover study (18). In a similar study, cetirizine was administered, 20 mg daily, for 2 days before and on the morning of testing. Eosinophil infiltration was decreased by approximately 80% in ragweed-sensitive subjects with a history of cutaneous late-phase responses to this allergen (19). In cutaneous eosinophilia induced by intradermal injection of PAF, significant inhibition of eosinophil migration was observed in patients pretreated with cetirizine (20). This effect of cetirizine could not be attributed to its H₁-activity, because cetirizine does not block histamine-induced eosinophil infiltration.

In regard to this anti-inflammatory effect in the lungs, Redier et al. made a randomized, double-blind, placebo-controlled trial of the effect of cetirizine on cellular recruitment in dual asthmatic responders 24 h after allergen inhalation challenge. Twelve allergic asymptomatic asthmatic subjects were selected and treated with either cetirizine (15 mg twice daily) or placebo. The main effect of cetirizine was to reduce the total numbers of all inflammatory cells in the bronchial wash significantly. The effect on eosinophil recruitment was particularly marked (Fig. 6). In contrast, the number of all cells in the later alveolar washings from the cetirizine group did not significantly differ from the number of inflammatory cells in lavage samples from the placebo group (21). Cetirizine did not influence the degree of bronchoconstriction in this study, but this could be explained by the fact that the PC₂₀ allergen was increased after cetirizine administration in three of the six subjects tested in order to get a significant late-phase reaction.

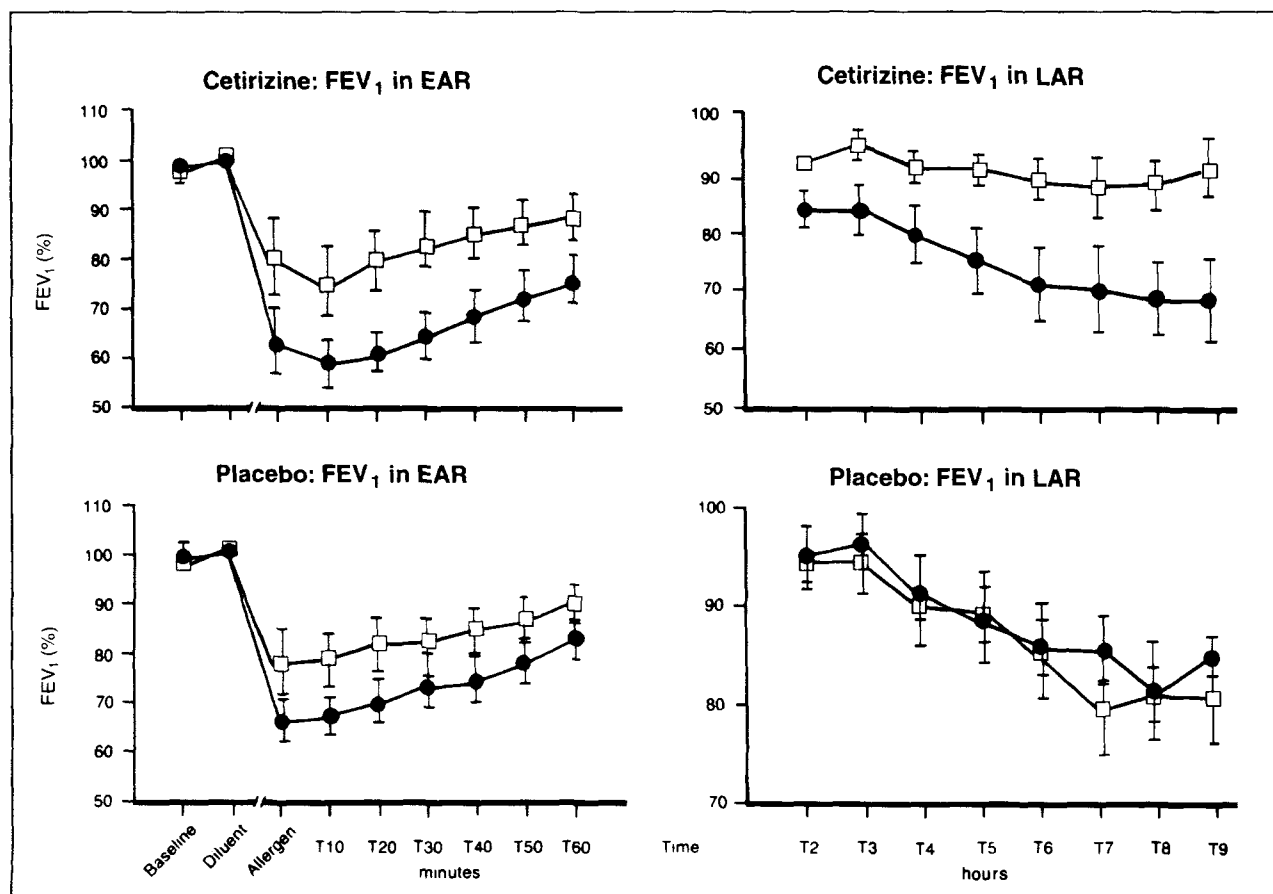


Fig. 5. Results of bronchoprovocation after treatment period on FEV₁ (%) in early asthmatic reaction (EAR) and late asthmatic reaction (LAR) (mean $\pm$ SEM; $n = 8$). Circles, before treatment; squares, after treatment. With permission, Wasserfallen et al. (16).

The pathogenesis of exercise asthma is poorly understood, although airway water loss is a potent stimulus in this condition (22). The effect of cetirizine was examined in both exercise- and antigen-induced asthma in a double-blind, randomized, placebo-controlled, crossover trial by Gong et al. (23). Oral cetirizine (5, 10, and 20 mg daily) was compared with oral albuterol (4 mg daily). Neither

drug inhibited exercise-induced bronchospasm. Furthermore, cetirizine failed to decrease bronchial sensitivity to inhaled allergen in 8/10 subjects. This study was confirmed by another in which cetirizine given orally twice daily for 1 week did not affect base-line FEV₁, or inhibit exercise-induced bronchoconstriction. However, inhaled cetirizine (5 and 10 mg/ml) given through a Wright nebulizer did confer a statistically significant protective effect on the exercise-induced fall in FEV₁ in 6/8 patients. There were no significant differences between the two doses of cetirizine (Fig. 7). Finally, inhalation of cetirizine (10 mg/ml) displaced the geometric mean PC₂₀ histamine 13.1-fold to the right, as compared with placebo (24). The disappointing results with oral cetirizine may be related to failure to achieve sufficient concentration at lung H₁-receptor sites. Inhalation of cetirizine may provide sufficient local drug concentration.

Various clinical studies have been undertaken during a pollen season to assess the efficacy of antihistamines in day-to-day allergen-induced asthma. One such study enrolled young adults with grass-pollen allergy who had between three and five asthma episodes weekly. For each patient, the

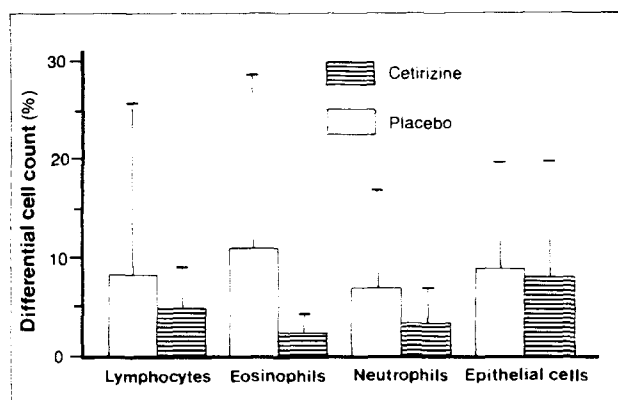


Fig. 6. Differential cell count of bronchial sample of BAL. With permission, Redier et al. (21).

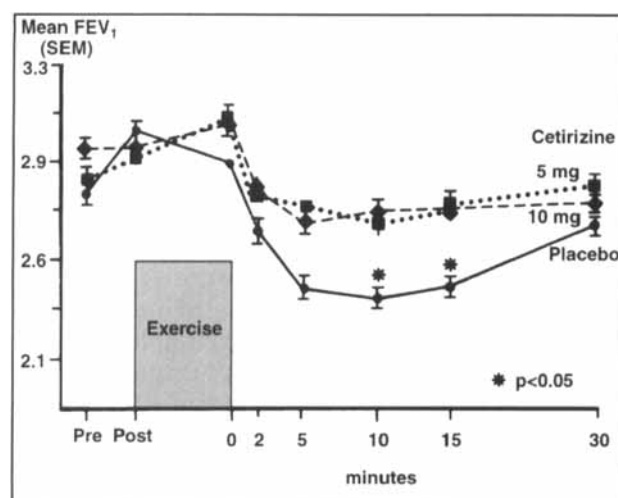


Fig. 7. Inhibition of fall in FEV₁ after exercise by inhaled cetirizine (5 and 10 mg/ml), as compared with placebo. There was no statistically significant difference between 5 and 10 mg of cetirizine. With permission, Ghosh et al. (24).

severity of the disease was assessed by the investigator at the initial visit and 14 days later. Patients also kept a daily diary to record their symptoms. Treatment with cetirizine 15 mg daily for 2 weeks produced a marked lowering of pulmonary symptoms. The use of other medications, including β_2 -agonists and steroids, was significantly reduced from the placebo group (25) (Table 1).

Bousquet et al. (26) performed a similar study of 1 month duration using 97 grass-pollen-allergic patients with mild asthma of recent onset. Cetirizine administered twice daily at 10 or 15 mg for 4 weeks was compared with terfenadine 60 mg twice daily. There was no placebo group. Cetirizine was found to be more effective than terfenadine (60 mg twice daily) in the control of seasonal asthma symptoms. The 15-mg, twice-daily dose was the most effective, and most asthma symptoms (wheezing, dyspnea, coughing) were eliminated in approximately half of those subjects taking the higher dose of cetirizine. Cetirizine also reduced bronchodilator use, although this finding was not statistically significant. In terms of side-effects, somnolence was reported by some subjects taking cetirizine, but this, too, was not statistically significant. A similar study also concluded that cetirizine could prevent exacerbation of seasonal asthma caused by grass pollen (27).

A study in the USA investigated the safety and efficacy of cetirizine in the prophylactic management of patients with seasonal allergic rhinitis and asthma. It began before the autumn pollen season. The randomized, placebo-controlled, double-blind trial was conducted over a 6-week period. Both groups (93 in each) had comparable symptoms at

Table 1. Self-evaluation by patient. With permission, Bruttman et al. (25)

	Placebo	Cetirizine	P
Rhinitis: mean weekly score/patient			
Week 1	15.10±3.31	12.4±3.3	<0.001
Week 2	Not calculated*	3.4±5.2	
Conjunctivitis: mean weekly score			
Week 1	14.62±3.5	12.0±3.7	<0.005
Week 2	Not calculated*	4.2±4.1	
Pulmonary score: mean weekly score			
Week 1	14.52±7.0	8.9±6.4	<0.001
Week 2	Not calculated*	5.8±4.5	
Morning peak flow			
On day 7: mean±SD	388.1±80.2	455.0±83.8	<0.005
Evening peak flow			
On day 7: mean±SD	383.3±81.6	460.7±78.6	<0.001
β_2 consumption: mean number of puffs/week			
Week 1	34.0±13.2	20.6±13.9	<0.005
Week 2	Not calculated*	17.0±11.0	
Terfenadine: between V ₁ and V ₂			
Number of patients	14	2	<0.001
Satisfied patients			
Number	3	20	<0.001
Corticosteroids			
Number of patients	22	4	<0.001
Number of dropouts for inefficacy	23	5	<0.001

* Not calculated because of high number of dropouts (23 patients among 29).

base line, but patients in the placebo group experienced worsening of symptoms as the trial progressed. Cetirizine (10 mg daily) improved both rhinitic and asthma symptoms and remained significantly better than the placebo for all weeks (except week 3) of the study. Twenty-four placebo and nine cetirizine group patients failed to complete the trial. Both treatments were well tolerated (28). This study concluded that cetirizine given as a prophylactic can safely benefit patients with mild to moderate asthma concomitant with seasonal allergic rhinitis.

In summary, antihistamines rarely exacerbate asthma. Indeed, most studies suggest they may be used in this condition. The second-generation drugs show great promise in this regard, given their increased H₁ specificity and safety over the older drugs. In particular, their lack of anticholinergic effects should remove one barrier which discouraged use of the first-generation medications. It can be envisaged that administration of the newer antihistamines in mild to moderate asthma would block the effects of histamine released spontaneously or after allergen exposure or exercise. Moreover, their use may allow the dosage of other asthma treatments to be safely decreased. The limited number of studies done to date with cetirizine indicate that it may be included in the arma-

mentarium for mild asthma therapy, although more studies comparing it with more established and conventionally prescribed agents are necessary to confirm this.

Round-table discussion

Simons: Jean Bousquet (26) used terfenadine in his control group and compared this with cetirizine. Do you think it's a problem, not having placebo controls?

Meltzer: Yes, I feel it is valuable to have a standard agent for comparison in the evaluation of a drug's effect; i.e., the placebo-treated patients. US studies include placebo-treated groups more regularly than the European studies.

Simons: I agree. We heard two studies in your presentation, Jean Bousquet's and one other (27), both of which had no placebo control. I think this is a problem because these medications look better when there is no placebo control to compare them with. We all see improvements of 20, 40, or even 50% given by placebo in, for example, rhinitis studies.

Rihoux: I think that you have to remember that the pollen-sensitive asthmatic subjects in the Bousquet study also had hay fever. The placebo-group patients would therefore tend to dropout because of nose-related symptoms. We are therefore obliged to use terfenadine to ensure we do not get patients leaving the study early because of uncontrolled hay fever symptoms.

Meltzer: I understand your comments and can review for comparison how we in the USA deal with our placebo-group patients in both seasonal rhinitis and asthma studies. Firstly, many of these patients do not drop out of these studies. Secondly, even if they do, this fact can be used as a measure of efficacy for a given medication. Thirdly, the use of rescue medications can also be a useful parameter of efficacy. Institutional review boards are often concerned about placebo-group patients and want some backup medication such as a β -antagonist, a decongestant, or another antihistamine. This issue is important because the FDA [US Federal Drug Administration] will often not consider studies very seriously without a placebo control.

Simons: I think that the use of rescue medications as an index of improvement or lack of the same is a really important point in many of the big studies

in the USA and represents a major advantage. In asthma studies, this information is almost as important as the FEV₁ data.

Meltzer: Yes. It would also help us to answer the question about whether patients who have allergic rhinitis get sleepy.

Broide: If I understood your slide correctly, it looked as though in one study an inhaled antihistamine worked better at inhibiting antigen-induced bronchoconstriction than an oral antihistamine. Are you aware of any clinical studies which have looked at the usefulness of inhaled preparations in, for example, day-to-day asthma?

Meltzer: We see similar improvements with the use of an inhaled antihistamine for exercise-induced asthma and I think this subject is an interesting one. We are all aware of the use of intranasal antihistamines where the topical application gets right to the problem area and allows the use of much lower drug doses. Therefore, we might be able to increase efficacy and reduce side-effects. This is an area deserving further exploration.

Rihoux: Is there any evidence for the development of tolerance to the bronchodilator effect of an antihistamine?

Meltzer: I'm unaware of any reports. Do you know of any?

Rihoux: I've only heard anecdotal reports.

De Vos: Ghosh et al. performed two studies, one using PAF-induced bronchospasm (13) and another with histamine- and leukotriene (LT)-induced bronchospasm (29). Cetirizine had some protective effect on PAF-induced bronchoconstriction, but this was not significant, and there was only a small protective effect against the LTD₄ bronchoconstriction. The protective effect of cetirizine against histamine-induced bronchoconstriction was twofold higher following a single dose than after 1 week of daily treatment with cetirizine.

Simons: Did you monitor compliance adequately?

De Vos: Yes, we did. I would also like to comment on one other clinical trial in asthma that wasn't mentioned in Dr Meltzer's talk. We enrolled children with perennial asthma in a large European study. There were 100 children in each group, in each of which cetirizine was compared with cromoglycate or placebo. We found cetirizine had a significantly better effect than either cromoglycate

or placebo in reducing the incidence of asthma crisis in these children (30).

Rihoux: One more comment about the use of terfenadine in the control group in the pollen-induced asthma study. Another reason for using another antihistamine in comparison with cetirizine is to show that any improvement in asthma is not due to an improvement in rhinitis. The patients taking terfenadine may show an improvement in their rhinitis with no asthma improvement. I think that this is telling us something.

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