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Antihistamines in the treatment of asthma

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Antihistamines were investigated for use in asthma shortly after discovery over fifty years ago. Earlier compounds proved ineffective because of side effects: this class of drugs was not thought useful for asthma, and were actually considered contraindicated. More recent drugs have greater potency, fewer side-effects, and no evidence of adverse effects in asthma. There are some studies showing second generation antihistamines, especially cetirizine, improve certain parameters of asthma.

History of the controversy

The use of antihistamines in asthma has long been controversial. Herxheimer (1) in 1949 showed the beneficial effect of antihistamines in asthma management. Levy and Seabury reported bronchospasm with antihistamine use in 1947 (2). Schuller (3, 4) in 1983 reported bronchoconstriction with antihistamine use in children with asthma. Her reports led to the warning that antihistamines should not be used in asthmatic patients because of the concern that they may thicken mucus secretions and increase bronchoconstriction (5). In 1988, the American Academy of Allergy and Immunology issued a Position Paper recommending that the warning be removed from antihistamine labeling and that antihistamines be prescribed to asthmatics when indicated (6). A 1991 survey of pharmacists revealed that 48% of them advised their asthmatic customers to avoid antihistamines and 75% of them believed that antihistamines would worsen asthma symptoms although sufficient clinical data to support this is lacking (7). In 1995 a task force on practice parameters for the diagnosis and treatment of asthma again reiterated that antihistamines can be used safely in most patients with asthma (8).

The early antihistamines were not valuable in the treatment of asthma because they were not effective in the doses recommended for allergic rhinitis, higher doses caused intolerable side effects, and side effects limited their use intravenously or via aerosol (5, 9–11). There is now evidence that some of the newer antihistamines may be useful in the treatment of asthma (5, 9–13). In this article we have briefly reviewed the history of research in antihistamine use in asthma. We have focused on articles published within the past ten years, especially those regarding second generation drugs, and articles written in English. Many reports have utilized acceptable standards of clinical investigation including blinding and controls. This concept was foremost in our evaluation and was the basis for our tabular review of key papers listed in Table 1. Obviously readers should consult the original articles for more specific details. We acknowledge that some classic articles may have been inadvertently omitted.

The role of histamine in asthma

In order for H_1-antihistamines to have any role in the management of asthma it stands to reason that histamine must be involved in the pathogenesis of asthma. There is ample evidence that histamine has a role in bronchial asthma (14).

Histamine as a mediator causes smooth muscle contraction, increased mucus secretion, increased vascular permeability resulting in mucosal edema, and parasympathetic nerve stimulation (5, 9–11, 14–18). Numerous stimuli cause the release of histamine from basophils and mast cells (19). The early- and late-phase reactions to antigen bronchial challenge mimic the phases of asthma. The early-phase reaction is due mostly to bronchoconstriction;

Table 1. Selected reports of controlled studies longer than a week for evaluating H_1-antihistamines in bronchial asthma

Drug	Study design	Daily dose (mg)	Duration	N	Asthma severity	Symptoms	PFTs	Bronchial reactivity	Rescue drug use	Signif.	Comments	Ref.
K	DB, RD, PL	2	26 wk	69	Mild & moderate	Improved	↑	ND	↓	Yes	Decreased use of theophylline	43
K	DB, PB, CO	2	24 wk	47	Moderate to severe	No Δ	ND	ND	No Δ	No	Children 2–6 years of age	46
K	DB, PB	2	52 wk	445	?	Improved	No Δ	ND	↓	Yes	Effect equal to cromolyn	47
K	DB, PB	2	12 wk	40	Moderate	Improved	No Δ	ND	↓	Yes		120
T	PB, DB, CO, RD	240	4 wk	42	Severe	No Δ	No Δ	ND	No Δ	No	Nocturnal awakening ↓	61
T	PB, DB, CO, RD	240	4 wk	10	Mild	ND	No Δ	No Δ to methach	ND	No	High drug dose	62
T	PB, DB, CO	240	2 wk	46	Mild	Improved	↑	ND	↓	Yes	High drug dose	68
T	PB, DB, CO	540	4 wk	18	Mild	Improved	↑	No Δ	↓	Yes	Very high drug dose	69
A	PB, DB, CO, RD	20	3 wk	20	?	No Δ	No Δ	↓ To histamine	ND	No	Children 6–15 years old	77
A	PB, DB, CO	10 or 30	4 wk	12	Mild	No Δ	ND	↓ To allergen	No Δ	Yes	10 mg took longer to work	79
L	PB, DB, CO	10	8 wk	17	Moderate	No Δ	No Δ	↓ To histamine	No Δ	No	Trend in favour of L	80
L	PB, DB, CO	20	4 wk	35	Moderate to severe	Slightly improved	No Δ	ND	No Δ	No	↑ PEFR initially only	82
AZ	DB, PB, CO, RD	17.6	2 wk	10	Mild	ND	↑ FEV_1	↓ to histamine	ND	No	No effect against LTC_4	97
AZ	DB, PB, PL	8.8	7 wk	24	Mild to moderate	Improved	↑ PEFR	↓ to histamine	↓	Yes	Bitter metallic taste	105
C	PB, DB, RD, PL	10	6 wk	93	Mild to moderate	Improved	No Δ	ND	↓	Yes	Allergic rhinitis & asthma pts	12
C	DB, PL	20 or 30	2 wk	80	Mild	Improved	↑ PEFR	ND	No Δ	Yes	T given to controls	55
C	DB, PL, RD	20	6 wk	43	Mild	Better	Better	ND	Less	Yes	T given to controls	57
C	DB, PB, PL, RD	15	2 wk	57	Mild	Worsened with PB	Worsened with PB	ND	↑ with PB	Yes	Seasonal symptoms	116
C	DB, PB, PL, RD	10–30	12 wk	348	Mild to moderate	↓ Asthma days	ND	ND	↓	Yes	Equal to cromolyn	115

Drugs: K = ketotifen, T = terfenadine, A = astemizole, L = loratadine, AZ = azelastine, C = cetirizine.
ND = not done or no data available. N = number of subjects taking H_1-antihistamine under study.
Study design: DB = double-blinded, PB = placebo-controlled, CO = cross-over, RD = randomized, PL = parallel.

the late-phase reaction is due to the inflammatory reaction that has developed over time. Plasma histamine and urinary methyl-histamine (a metabolite) levels are elevated in both the early- and late-phase asthmatic responses to antigen challenge; this has also been shown in patients with spontaneously appearing asthma, exercise-induced asthma, and after inhalation of hypotonic or hypertonic solutions (5, 9, 20). Lung biopsies of allergic and nonallergic asthmatics show mast cells (21, 22). Bronchoalveolar lavage (BAL) fluids obtained during the late phase reaction have increased basophils (23). The BAL fluids from asthmatics have increased levels of histamine which correlates with nonspecific bronchial hyperreactivity (24). Histamine inhalation causes bronchospasm in most individuals, but the response in asthmatic patients is increased or hyperreactive (15, 16). Histamine may also have a role in immunomodulating the immunoglobulin E (IgE) immune response (25).

A review of the use of antihistamines in asthma

The first clinically useful H_1-receptor antagonist, *pyrilamine maleate*, described by Bovet and colleagues (26) in 1944 was soon followed by *phenbenzamine, diphenhydramine, tripelennamine*, and others (13). These antihistamines have been categorized as the first generation or sedating antihistamines because they are lipophilic and cross the blood-brain barrier with ease thereby causing central nervous system effects such as drowsiness. They also have anticholinergic and antiserotonergic effects.

The newer or second generation antihistamines were introduced in the 1980's beginning with *terfenadine* and followed by *astemizole, loratadine,* and *cetirizine*. These antihistamines are relatively lipophobic and highly protein bound and therefore do not cross the blood-brain as easily. They are less sedating, lack anticholinergic and antiserotonergic effects (26).

With the advent of the knowledge that histamine plays a role in bronchial asthma 14), it was only logical to assume that antihistamines may have a beneficial therapeutic effect. Herxheimer was the first to confirm this when he reported on the bronchodilatory effects of *chlorpheniramine* (1). This, however, did not appear to be a class specific benefit, as Levy and Seabury (2) found *diphenhydramine* 100 mg orally to be bronchospastic in some patients. Later studies suggested *chlorpheniramine* (27, 28) and *clemastine* (29, 30) to have bronchodilatory effects, but were of limited benefit in preventing allergen-induced bronchoconstriction secondary to their sedative and anticholinergic effects at higher doses. *Brompheniramine* (4) was subsequently reported to cause bronchoconstriction. Since clinical efficacy in asthma was difficult to establish, the use of these older H_1-antihistamines was discouraged (31).

With the introduction of the new H_1-antihistamines with increased potency and specificity, the use of this class of medications in asthma is being reassessed. The most extensive comparative study of antihistamines in patients with asthma has been performed by Wood-Baker & Holgate (32). They conducted a single-blind, placebo-controlled study to assess the effect of the antihistamines *astemizole, brompheniramine, cetirizine, chlorpheniramine, clemastine, cyproheptadine,* and *terfenadine* versus placebo on histamine- and methacholine-induced bronchoconstriction. Study drugs at the manufacturer's recommended dose were given as a single dose 2–4 hours prior to bronchial challenge with histamine or methacholine, and the provocation concentration required to cause a 20% fall in FEV_1 ($PC_{20}FEV_1$) was determined. A minimum 2 week wash-out period between drugs was required and astemizole was the final drug to be evaluated. The geometric mean $PC_{20}FEV_1$ for each pre-treatment modality is shown in Table 2. The bronchodilator action of each study drug expressed as percent increase in FEV_1 over placebo is shown in Fig. 1.

Table 2. Schedule of H_1-receptor antagonist pretreatment and the effect on histamine and methacholine $PC_{20}FEV_1$ values. Reproduced with permission of Mosby-Year Book, Inc. from J Allergy Clin Immunol 1993;91;1007, Table II (32)

Pretreatment	Dose (mg)	Time after dosing to challenge (hr)	Geometric mean $PC_{20}FEV_1$	
			Histamine arm (mg/ml)	Methacholine arm (mg/ml)
Placebo	–	2	0.51	0.30
Chlorpheniramine	4	2	1.26	0.54
Terfenadine	60	2	10.31	0.32
Brompheniramine	4	4	1.11	0.45
Cetirizine	10	2	55.68	0.36
Cyproheptadine	4	4	1.70	0.41
Clemastine	1	4	2.66	0.53
Astemizole	10	2	1.91	0.44

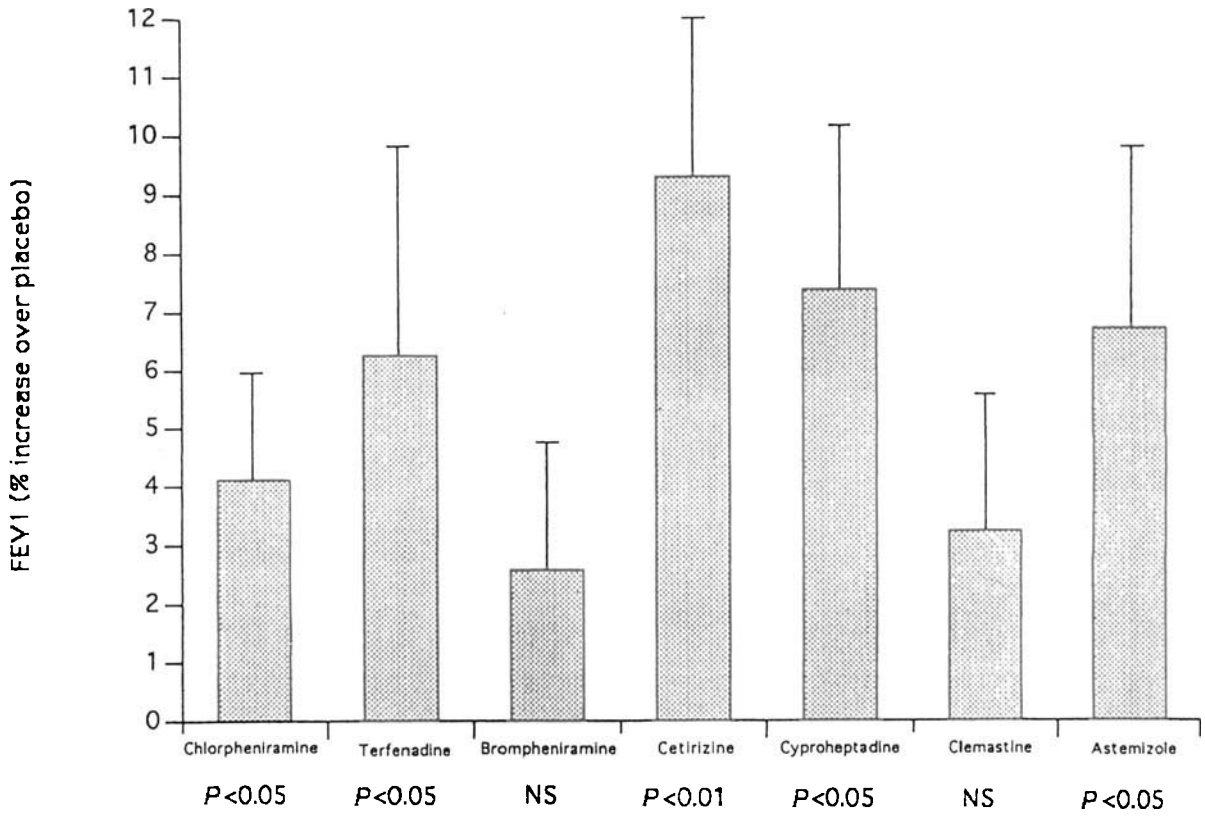

Fig. 1. The bronchodilator action of H_1-antihistamines is expressed as the percentage increase in baseline FEV_1 after administration of active drug compared with placebo. Each bar represents the mean±s.e.mean for 18 patients. Reproduced with permission of Mosby-Year Book, Inc. from J Allergy Clin Immunol 1993:91:1008, fig. 1 (32).

None of the antihistamines studied changed methacholine-induced bronchoconstriction. Cetirizine and terfenadine had greater effects than the other antihistamines in displacing histamine-induced bronchoconstriction, with cetirizine giving better protection than terfenadine. The relative protection given by each antihistamine, expressed as a mean concentration ratio, against histamine- and methacholine-induced bronchoconstriction is shown in Fig. 2. Loratadine and ketotifen were not evaluated in this study.

Ketotifen

This sedating antihistamine may also act as a membrane stabilizer inhibiting cellular degranulation and histamine release (33, 34). Numerous studies have evaluated the effect of ketotifen in asthma. Bronchial mucosa from atopic, mild to moderate asthmatics treated with ketotifen had significantly less eosinophils, neutrophils, and activated T lymphocytes than before treatment (35). Ketotifen corrects the decreased methyltransferase and increased phosphodiesterase activity observed in asthmatics; doing so allows intracellular cAMP accumulation thereby decreasing the secretory process, and enabling normalization of beta-receptor expression (36–38). This drug has a stimulating effect on suppressor T-cells leading to a decrease in leukotriene B4 and thromboxane A2 in bronchoalveolar lavage fluid (37, 39).

Asthmatic children were able to decrease their oral doses of theophylline with less worsening of symptoms, and have less bronchial hyperreactivity with ketotifen therapy (40). Ketotifen has a steroid sparing effect on steroid dependent asthmatics (41, 42). There are studies showing both the effectiveness and ineffectiveness of ketotifen in asthma. A double-blind, placebo controlled randomized study involving 138 children showed earlier improvement and greater changes in pulmonary function, decreased use of concomitant medications, better patient global evaluation scores, better physician clinical evaluations, decreased incidence of emergency room visits for asthma, and decreased incidence of upper respiratory tract infections (43). Although it has been shown that ketotifen in infants and young children with non-infected wheezy bronchitis and bronchial asthma has some temporizing benefit (44) others have shown that in younger children, aged 1 to 6, ketotifen was no better than placebo (45, 46).

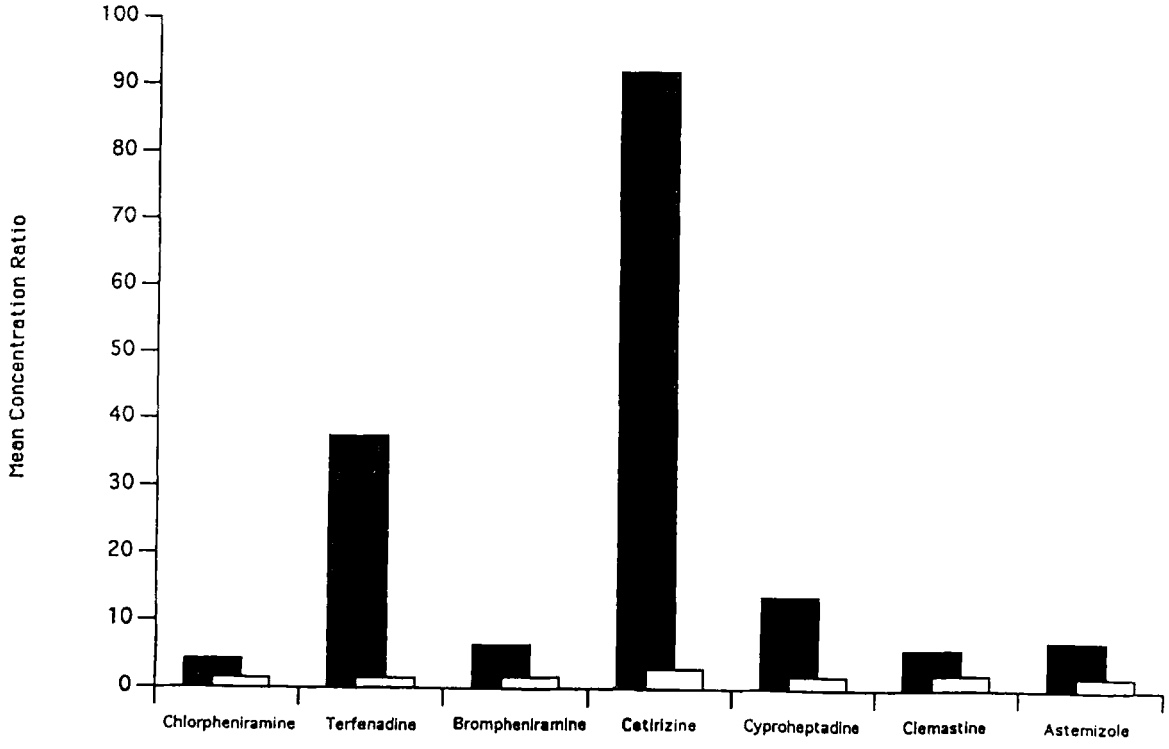

Fig. 2. The protective efficacy of antihistamines against the airway response to histamine (shaded bars) and methacholine (open bars) is expressed as a mean concentration ratio for the nine subjects who completed the protocol for each inhalation challenge. Reproduced with permission of Mosby-Year Book, Inc. from J Allergy Clin Immunol 1993:91:1010, fig. 10 (32).

The largest, double-blind placebo controlled study evaluating the effects of ketotifen in atopic asthmatics was conducted in 445 patients. Ketotifen at a dose of 1 mg twice a day decreased concomitant medication use without increasing symptoms or decreasing pulmonary function (47). Bronchial hyperreactivity was diminished with ketotifen therapy when evaluated by histamine PC_{20} but not methacholine (48–50). Ketotifen has also been shown to prevent the onset of asthma in children with atopic dermatitis (51, 52), "preasthmatic" children, infants with a family history of major allergy and elevated serum IgE (53).

Overall ketotifen appears to be an effective adjunctive treatment for asthma in patients above six years of age. Its use as a "prophylactic" agent in infants at risk for developing asthma cannot yet be fully endorsed. Ketotifen has become a popular drug in the management of asthma, especially in Japan (38). When submitted to US regulatory authorities for approval for use in the treatment of asthma during the past decade, it was concluded that definitive trials showing its efficacy for this purpose were not available. To our knowledge more recent reports have not be reevaluated.

Terfenadine

Terfenadine, the first non-sedating antihistamine (54), has been shown *in vitro* to inhibit the release of histamine from mast cells. This inhibitory effect appears to be mediated by the prevention of intracellular calcium ion uptake and release, the inhibition of protein kinase C translocation, and adenylate cyclase activation resulting in increased cyclic AMP (38).

Terfenadine has had variable success in the treatment of asthma and often at doses much higher than those recommended by the manufacturer for rhinoconjunctivitis. In several studies of cetirizine in asthma, terfenadine at a dose of 60 mg twice a day was given to the control group for the treatment of nasal and ocular symptoms because of the belief that it had no effect on the underlying asthma (55–57). Later, however, a single dose of terfenadine 60 mg was shown to increase the forced expiratory volume in 1 second (FEV_1), protect against histamine-induced bronchoconstriction, and not protect against methacholine-induced bronchoconstriction (32, 58–60).

At a dose of 120 mg twice daily for 4 weeks, terfenadine as an addition to maintenance asthma treatment, in a double-blind, randomized, placebo-controlled crossover trial in 42 severe chronic asthmatics had no significant therapeutic benefit (61). Another study using the same dose and duration of terfenadine showed no significant differences in FEV_1 or the provocative concentrations of methacholine causing a 20% fall in FEV_1 (62).

Similarly, there was no significant benefit in the diurnal variation of the peak expiratory flow rate (63), nor the late phase response to allergen inhalation challenge in atopic asthmatics (64). The immediate response to bronchial allergen challenge can be attenuated by terfenadine but the effect was small and did not correlate with dose (65).

Several published studies have shown contrasting results where terfenadine has produced significant bronchodilation with increases in FEV_1, and/or the provocative concentrations of histamine causing a 20% fall in FEV_1 (38, 58–60, 66, 67). Taytard et al. (68) found that terfenadine 120 mg twice daily for two weeks in 46 patients in a double-blind, placebo-controlled study resulted in reduced symptoms, improved pulmonary function tests, and reduced use of beta-agonists. In another report terfenadine 180 mg three times a day was given to 18 mild, grass pollen sensitive asthmatics in a 9 week, double-blind, placebo controlled, crossover study (69). Terfenadine significantly reduced symptoms of cough and wheezing. There was also improvement in symptoms of breathlessness and chest tightness but the difference did not reach statistical significance. Morning and evening peak expiratory flow rates improved statistically with therapy. Bronchodilator use decreased by 40% without significantly affecting bronchial hyperreactivity.

Terfenadine although potentially of benefit in asthma therapy at much higher doses carries the risk of cardiac arrhythmias (70, 71, 72). Terfenadine is metabolized by hepatic P_{450} isoenzymes, and has marked interaction with certain macrolide antibiotics and antifungal agents. Simultaneous administration of these drugs results in accumulation of unmetabolized terfenadine, a compound with marked inhibitory effects on the cardiac I_K channel that may result in fatal arrhythmias. At conventional doses of 120 mg daily terfenadine seems ineffective in asthma.

Astemizole

Astemizole, another second generation antihistamine, differs in that it has a later onset of action and the longest half-life, approximately 13 days after chronic dosing (26). This long acting antihistamine is also relatively devoid of central, sedative and anticholinergic effects (73, 74). Clee et al. (73) observed that astemizole treatment with a daily 10 mg dose for one week conferred some protection against exercise-induced asthma, a benefit that persisted one week after discontinuing therapy. A 10 mg daily dose has been shown to antagonize histamine-induced bronchoconstriction (9, 75–77). A single dose of 10 mg of astemizole given to asthmatic patients resulted in increases in PC_{20} histamine that lasted 1–2 days (78). In a placebo-controlled, double-blind, crossover study of extrinsic asthma patients it was shown that allergen-induced bronchoconstriction was attenuated with single daily doses of 10 mg of astemizole after 28 days. This inhibition appeared within 7 days with 30 mg single daily doses (79). As with terfenadine, however, there is a concern about potential cardiac toxicity at higher doses of astemizole and of drug interactions (70, 71, 72).

Loratadine

This second generation antihistamine is similar to astemizole and terfenadine but unique because it can undergo hepatic metabolism by two isoenzymes of the P_{450} system (26). The effect of a daily dose of 10 mg of loratadine in 17 chronic, stable asthmatics on moderate doses of inhaled steroids trended towards better asthma control but did not reach statistical significance (80). In a randomized, double-blind, placebo controlled, crossover study of loratadine 10 and 20 mg for 3 days there was no evidence of bronchodilation 3 hours after the final dose (81). The efficacy of a higher dose of loratadine on moderate to severe asthmatics has recently been evaluated in 35 patients in a double-blind, placebo-controlled, crossover study (82). Loratadine 20 mg once daily or placebo was given for 4 weeks. Although loratadine was favored in the global assessment of efficacy the difference was not statistically significant. There was also no objective improvement in asthma control but PEFR did improve during the initial phase of treatment. A single 10 mg dose of loratadine in mild bronchial asthma patients did not significantly alter their spirometric parameters but did significantly reduce their bronchial response to histamine (83). Loratadine 30 mg had a protective effect on the late phase of allergen-induced bronchoconstriction but the sample size of this particular study was very small (84). In an open clinical trial where loratadine 10 mg was given as a single daily dose for 6 weeks, lung function parameters (vital capacity, FEV_1, peak flow, resistance) improved by up to 21%. Symptom scores improved and the use of inhaled sympathomimetics decreased (85). Loratadine does not appear to have a statistically significant beneficial effect in asthma.

Azelastine

Azelastine has potent H_1-receptor blocking activity (86) of long duration (87, 88) and several other interesting properties. In animal studies, azelastine inhibits leukotriene action by interfering with its synthesis and release (86, 89–91), inhibits mast cell

mediator release (92–94), and modulates anaphylaxis (90, 95, 96). In humans azelastine has been shown to inhibit histamine-induced (97–99) and allergen-induced (100, 101) bronchoconstriction after both a single dose and continuous treatment although it does not inhibit leukotriene C_4-induced bronchoconstriction (97) or the late-phase response to an allergen (102). Azelastine has been shown to significantly attenuate exercise-induced bronchospasm (103), and produce significant bronchodilation after a single oral dose in asthmatics (104) although, with continued administration, this bronchodilatory effect is not sustained (105). Asthma symptoms improved, there were fewer attacks, and concomitant medication use decreased when azelastine 4 mg twice a day for 2 weeks was given in a multicenter, double-blind, placebo-controlled, randomized study (106). Similarly, 4.4 mg twice a day for 7 weeks in a double-blind, parallel group, placebo-controlled study of patients with extrinsic asthma revealed decreased airway responsiveness to histamine, improved peak expiratory flow rates, decreased symptoms, and decreased use of inhaled bronchodilators (105). The most common adverse effect of azelastine is dysgeusia or a metallic taste in the mouth.

These limited trials infer that azelastine results in objective improvement in asthma control.

Cetirizine

A carboxylated, human metabolite of hydroxyzine (107), is another H_1-specific receptor antagonist. Cetirizine is possibly the most potent antihistamine, suppressing the skin wheal and flare response to histamine to a greater degree than any other H_1-antihistamine (32, 108). Cetirizine decreases the influx of inflammatory cells including eosinophils after antigen challenge in the skin, nose, conjunctivae and bronchi, as well as inhibiting the expression of intercellular adhesion molecule-1 on epithelial cells (109–113). Several studies have suggested its beneficial effect in the treatment of asthma (12, 55–57, 113–118), and some of these are listed in Table 1. Most of these trials utilized higher doses of the drug which may not be practical as there is a greater likelihood for sedation. We will focus on three recent reports that emphasized lower doses (12, 114, 115).

Cetirizine's significant bronchodilatory effect in patients with mild-to-moderate asthma (baseline FEV_1 between 50–80% of predicted value) was shown in a randomized, double-blind, placebo-controlled, crossover study that examined the effect of cetirizine on pulmonary function (114). Cetirizine 5, 10, or 20 mg orally with or without inhaled albuterol was given to 12 patients and pulmonary function parameters determined at several points over 8 hours. A significant increase in FEV_1, peak expiratory flow rate, and FEF_{25-75}, but not forced vital capacity relative to baseline and placebo was found with cetirizine. The 20 mg dose generally had a greater effect on FEV_1 than 10 or 5 mg. All 3 doses showed significantly greater increases than placebo in FEV_1 and FEF_{25-75} over 8 hours; and in PEFR over 7 hours. Albuterol's significant effect on the pulmonary function variables lasted only up to 5 hours (Fig. 3). Cetirizine

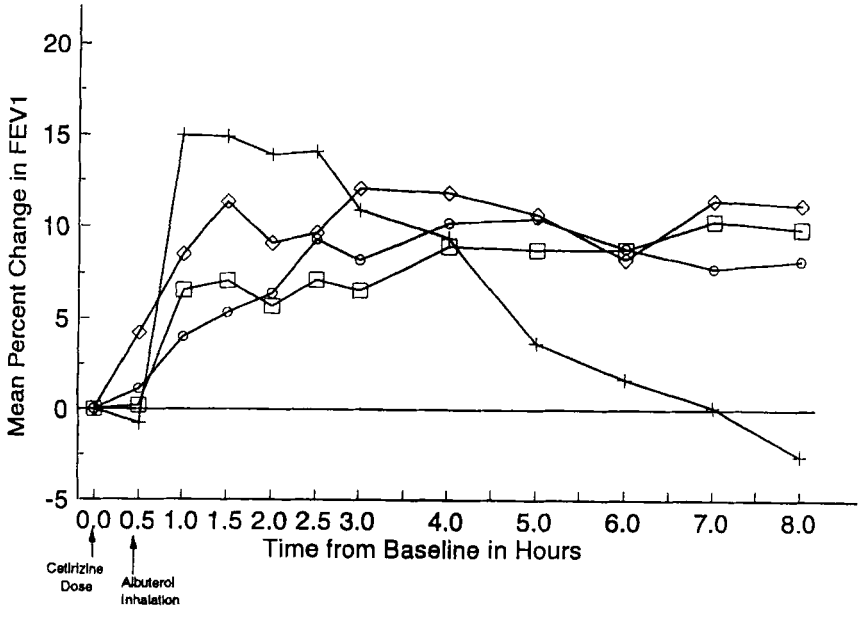

Fig. 3. Mean percent change in FEV_1 adjusted for baseline and placebo effect as a function of time after the administration of oral cetirizine, 20 mg (diamonds), 10 mg (squares), and 5 mg (circles) alone and after inhalation of albuterol 180 mcg alone (plus symbols) (N=12). Reproduced with permission of Mosby-Year Book, Inc. from J Allergy Clin Immunol 1995:96:177, fig. 1 (113).

did not inhibit the bronchodilatory effects of albuterol, did not worsen pulmonary function, and had an additive bronchodilatory effect with albuterol.

Kjellmann (115), in a study involving 348 children and adolescents with mild to moderate perennial asthma, compared the effects of cetirizine (10 to 30 mg daily depending on body weight) with cromolyn sodium and placebo. Cetirizine showed a statistically significant decline in total number of days with asthma and in beta-agonist use when compared with placebo. In this study cetirizine was at least as effective and cromolyn sodium.

A 6 week multicenter, randomized, double-blind, placebo-controlled parallel study compared the efficacy of cetirizine 10 mg versus placebo in 186 patients with seasonal allergic rhinitis and concomitant mild to moderate asthma (12). The top of Fig. 4 shows the mean changes from baseline

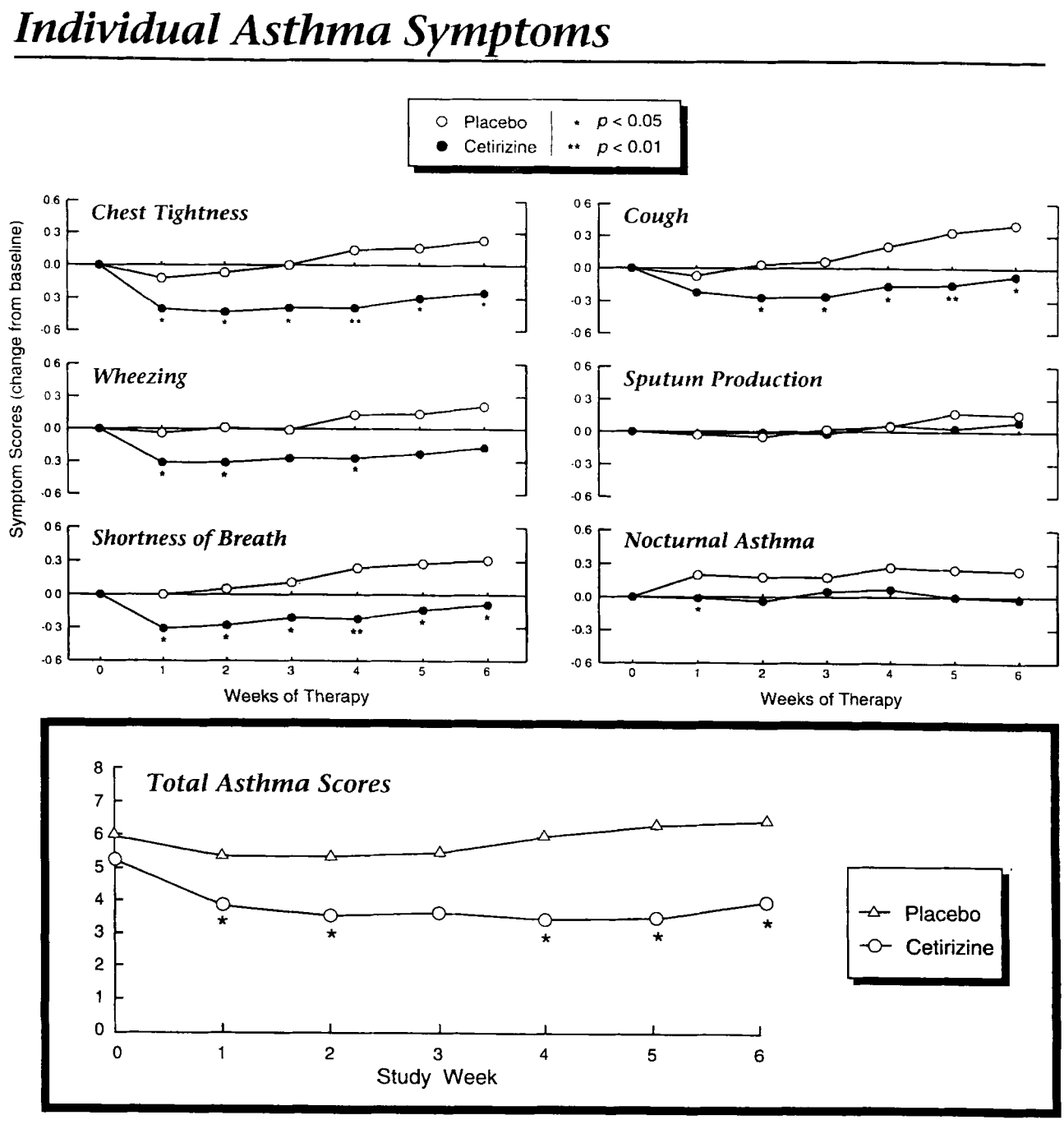

Fig. 4. Individual (top) and total (bottom) asthma symptoms. Significant differences for cetirizine (open circles) vs placebo groups (solid circles) for each week of evaluation are shown. Reproduced with permission of Mosby-Year Book, Inc. from J Allergy Clin Immunol 1995:95:928, fig. 2 (11).

for the individual asthma symptom scores; the bottom shows the mean total asthma symptom scores. Chest tightness, wheezing, shortness of breath, and cough improved in the cetirizine group but sputum production and nocturnal asthma did not significantly improve. Cetirizine treated patients had significantly lower total asthma symptom scores than placebo treated patients for most treatment periods. Daily peak expiratory flow rate measurements and weekly pulmonary function parameters did not change significantly between the two treatment groups. Bronchial hyperreactivity, as assessed by methacholine challenge was not performed. The cetirizine group used less albuterol inhalations than the placebo group, but this did not reach statistical significance. Cetirizine was rated significantly better than placebo in the global evaluation for rhinitis by both patients and investigators, but no significant difference between the treatment groups was found for asthma control. The incidence of fatigue and somnolence was greater in the cetirizine than placebo group, but this was mild to moderate and no patient in the cetirizine group discontinued treatment because of it.

Overall cetirizine at conventional doses of 10 mg daily provides symptomatic improvement for seasonal allergic rhinitis and asthma in patients suffering both conditions without significant changes in the pulmonary function parameters. Furthermore, the drug caused few side effects. Cetirizine was found to have no electrocardiographic effects at doses as high as 60 mg daily (119), and has no interaction with macrolide antibiotics, antifungals and other drugs.

Conclusion

The initial controversial history with regards to the use of antihistamines in asthma involved the older antihistamines with their sedating, anticholinergic and antiserotonergic effects. Although deemed safe for use in asthmatic patients because these drugs do not appear to worsen pulmonary function, they have not been recommended for asthma therapy. The second generation H_1-antihistamines, with their greater specificity and less sedating effects increased the interest in the use of this class of compounds for asthma. Terfenadine and astemizole require higher than recommended dosages to have a significant effect, but their risk for cardiotoxicity and drug interactions limits their use. Loratadine has not been shown to have a statistically significant benefit in asthma even at higher doses. Ketotifen has been shown to be beneficial in asthma, but is not available in the U.S.A., and as a sedating antihistamine its use may be limited secondary to this side effect. Azelastine, which also is not available in the U.S.A., appears to have a beneficial effect in asthma. Cetirizine which has recently been approved in the U.S.A. is promising as an adjunct in the treatment of asthma. At recommended doses for allergic rhinitis, cetirizine improves asthma symptoms, decreases rescue drug use, and does not worsen pulmonary function parameters. Short term cetirizine has some bronchodilatory properties. Despite the increasing number of good quality studies, more studies need to be performed before any specific antihistamine can be advocated for asthma therapy. At the present time, it is clear that at the recommended dosages antihistamines will not adversely affect asthma.

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