The comparative actions and adverse effect profile of single doses of H_1-receptor antihistamines in the airways and skin of subjects with asthma

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Background: *The development of potent H_1-receptor antagonists that are free of adverse effects has renewed interest in their use in the treatment of asthma.*
Methods: *We performed a study of the action of chlorpheniramine, terfenadine, brompheniramine, cetirizine, cyproheptadine, clemastine, and astemizole compared with placebo on histamine-induced skin wheals and bronchoconstriction in a single group of patients with asthma. Another group underwent methacholine bronchoprovocation.*
Results: *Antihistamine pretreatment increased mean baseline measurements of forced expiratory volume in 1 second (FEV_1) between 2.58% and 9.28% compared with placebo, which was significant for all drugs except brompheniramine and clemastine. Compared with placebo, all antihistamines provided significant protection against histamine-induced bronchoconstriction when measured as the provocation concentration required to cause a 20% fall in FEV_1; terfenadine and cetirizine provided significantly greater protection than other antihistamines. Protection against histamine-induced skin wheals, measured as the slope of the log concentration-response curve, was only significant for the new drugs, terfenadine and cetirizine. There was a good correlation between the protective effect of the drugs in the skin and airways ($r = 0.85$; $p < 0.01$). No significant difference in methacholine provocation concentration required to cause a 20% fall in FEV_1 values between treatments was found.*
Conclusions: *The new H_1-receptor antagonists terfenadine and cetirizine provided significantly better protection than the older antihistamines against the action of histamine in the skin and airways. None of the antihistamines showed evidence of anticholinergic activity in the asthmatic airways at the doses studied. (J ALLERGY CLIN IMMUNOL 1993;91:1005-14.)*

Key words: *Antihistamines, asthma, H_1-receptor antagonists*

The biogenic amine histamine was the first mediator to be implicated in the pathogenesis of asthma, shortly after its structural identification at the turn of the century.[1] The development of drugs capable of blocking the actions of histamine, particularly at the H_1-histamine receptor,[2] led to great enthusiasm for their use in the treatment of asthma. These drugs were shown to antagonize the bronchoconstrictor response to histamine in patients with asthma.[3] Later antihistamines also showed a bronchodilator action on resting airway tone.[4] Unfortunately, the initial optimism for their use, which was largely based on uncontrolled studies that relied on subjective changes in symptoms to monitor treatment response,[5-7] proved to be ill-founded. With the introduction of other treatments such as β-agonists, antihistamines as therapeutic agents for asthma were largely discarded. Indeed, because of the

Abbreviations used

FEV_1:	Forced expiratory volume in 1 second
ANOVA:	Analysis of variance
$PC_{20}FEV_1$:	Provocation concentration of agonist required to cause a 20% fall in the FEV_1 from baseline measurements
H_1:	Type I histamine receptor

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TABLE I. Characteristics of subjects with asthma

Subject	Sex	Age	Atopic	FEV_1	Predicted value (%)	$PC_{20}FEV_1$
Histamine bronchial challenge						
1	M	26	+	3.35	84	0.62
2	M	29	−	3.35	95	0.28
3	M	39	+	3.55	100	0.48
4	F	59	−	1.90	119	0.17
5	F	40	−	3.10	109	1.08
6	F	25	+	3.40	121	1.50
7	M	30	+	4.90	123	0.85
8	F	45	+	2.05	79	0.35
9	M	39	−	4.15	102	0.39
10	F	47	+	2.80	109	0.36
Mean ± SD		38 ± 11		3.26 ± 0.89	104 ± 15	GM = 0.50 GSD = 2.00
Methacholine bronchial challenge						
1	M	56	−	3.15	91	0.24
2	F	53	+	2.30	107	0.66
3	F	58	+	1.90	76	0.24
4	M	55	+	3.10	91	0.33
5	M	31	+	3.40	83	1.42
6	M	54	+	3.10	89	0.26
7	F	43	+	2.50	96	0.36
8	M	31	+	2.90	76	0.55
9	F	25	−	2.75	84	0.29
10	F	48	+	2.00	95	0.18
Mean ± SD		45 ± 1		2.71 ± 0.52	89 ± 10	GM = 0.40 GSD = 1.80

$PC_{20}FEV_1$ Provocation concentration of histamine causing a 20% fall in FEV_1 from post-saline measurement; *GM*, geometric mean; *GSD*, geometric standard deviation.

anticholinergic effects of many of these early drugs and their potential for "drying" airway secretions, their use in asthma was positively discouraged.[8] The therapeutic use of these antihistamines was further restricted by their adverse effect profile, particularly sedative and anticholinergic effects.

Encouraged by the protection afforded against the acute allergic response in other tissues (e.g., skin and nose), investigators have shown renewed interest in the development of H_1-receptor antihistamines, which are more potent[9, 10] and devoid of the dose-limiting adverse effects.[11] In asthma, a number of studies have shown that these new drugs are bronchodilators and also protect against the bronchoconstrictor action of exogenously administered histamine.[12, 13] This study aimed to provide a direct comparison of the action of old and new antihistamines in blocking the effects of histamine in the airways and skin of patients with asthma and to determine their anticholinergic action in the airways.

METHODS

Subjects

Twenty nonsmoking volunteers with stable asthma and a mean age of 41.6 years (range, 25 to 59 years) took part in the study; subjects were divided equally between the histamine and methacholine arms (Table I). Half the subjects were men and 70% atopic, defined as a >2 mm wheal response to at least two of a range of common allergens (Bencard, Brentford, England). Subjects had a history of dyspnea and wheeze of at least 2 years' duration, with a ≥20% variation in their forced expiratory volume in 1 second (FEV_1) either spontaneously or after use of bronchodilator aerosol. The overall mean FEV_1 was 2.98 L (range 1.90 to 4.90 L), which represents a mean of 98% (range, 76% to 119%) of predicted values. All had hyperresponsive airways, defined as a provocation concentration of histamine that reduced the FEV_1 by 20% from measurements taken after saline diluent administration of <8 mg/ml. In addition to inhaled β_2-agonists, all subjects were taking regular inhaled corticosteroids (range, 200 to 1500 μg of beclomethasone per day) as their maintenance treatment. Bronchodilators were withheld for 8 hours before each study day, whereas inhaled corticosteroids were

TABLE II. Schedule of H_1-receptor antagonist pretreatment and the effect on histamine and methacholine $PC_{20}FEV_1$ values

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[14]	4	2	1.26	0.54
Terfenadine[15]	60	2	10.31	0.32
Brompheniramine[16]	4	4	1.11	0.45
Cetirizine[17]	10	2	55.68	0.36
Cyproheptadine[18]	4	4	1.70	0.41
Clemastine[19]	1	4	2.66	0.53
Astemizole[20]	10	2	1.91	0.44

continued at their usual dose, which remained constant throughout the study period. Subjects gave written informed consent, and the study was approved by the Southampton University and Hospitals Ethics Committee.

Study design

Subjects participated in a single-blind, placebo-controlled study with two arms, which allowed assessment of the effect of the antihistamines and placebo on histamine- and methacholine–induced bronchoconstriction. In the histamine arm, subjects also underwent skin prick testing with histamine to enable a comparison of the drug effect in the skin and airways. Study drugs were supplied as single tablets, which contained the manufacturer's recommended dose for administration at a single time point at the time of the study. Before arrival in the department, subjects were predosed with placebo or active drug, which allowed peak plasma concentrations to be achieved before bronchial challenge. The predosing interval was based on the known pharmacokinetic profile of each drug[14-20] (Table II). Each subject attended the department on 8 study days, which were separated by a minimum 2-week washout period, and was dosed in descending order as shown in Table II.

Agonist solutions

Histamine acid phosphate (BDH Ltd, Poole, England) was dissolved in 0.9% sodium chloride (saline solution) buffered to pH 7.4 and stored as a stock solution of 64 mg/ml in 4 ml aliquots at −20° C. On each study day, stock solution was thawed immediately before use and diluted with saline solution to produce a range of doubling concentrations from 0.03 to 32 mg/ml. Methacholine (Sigma Chemical Co., Ltd, Poole, England) was also dissolved in saline solution to produce a stock solution of 64 mg/ml and similarly stored until use. Immediately before use the stock solution was thawed and diluted with saline solution to produce doubling concentrations of 0.03 to 32 mg/ml.

Bronchial challenge

Measurements of FEV_1 were made with a dry bellows spirometer (Vitalograph, Buckingham, England), and the highest measurement of three attempts at each time point was used for analysis. Solutions were administered with an Inspiron Mini-neb nebulizer (C. R. Bard International, Sunderland, England) driven by compressed air at 8 L/min from a starting volume of 3 ml. Under these conditions the nebulizer produced a mass median particle diameter of 4.7 μm and had a delivery rate of 0.33 ml/min. For all solutions, subjects were instructed to take 5 breaths from functional residual capacity to total lung capacity while wearing a nose clip, according to a method modified from that of Chai et al.[21] On each study day after a 10-minute rest period, two baseline measurements of FEV_1 were performed 5 minutes apart. Providing that these did not vary by more than 10%, when subjects were asked to return on another occasion, subjects proceeded to bronchial challenge. Subjects initially inhaled saline diluent with FEV_1 measurements at 1 and 3 minutes after inhalation. If the measurements after saline diluent administration did not vary by more than 10% from baseline, subjects inhaled increasing concentrations of histamine or methacholine. Further measurements of FEV_1 were made at 1 and 3 minutes after inhalation until a fall in FEV_1 of 20% or greater than the lower measurement after saline diluent administration had been achieved or the maximum concentration of agonist had been inhaled. After completion of the challenge any residual airflow obstruction was reversed with inhaled salbutamol (200 μg).

Skin prick testing

Immediately after the bronchial challenge with histamine, subjects underwent histamine skin prick testing. Doubling concentrations of histamine acid phosphate from 2 to 32 mg/ml were applied to the volar surface of the forearm as single drops of solution, and the skin was pierced with individual prick lancets (DHS Miles Laboratories Ltd., Slough, England). Skin wheal areas

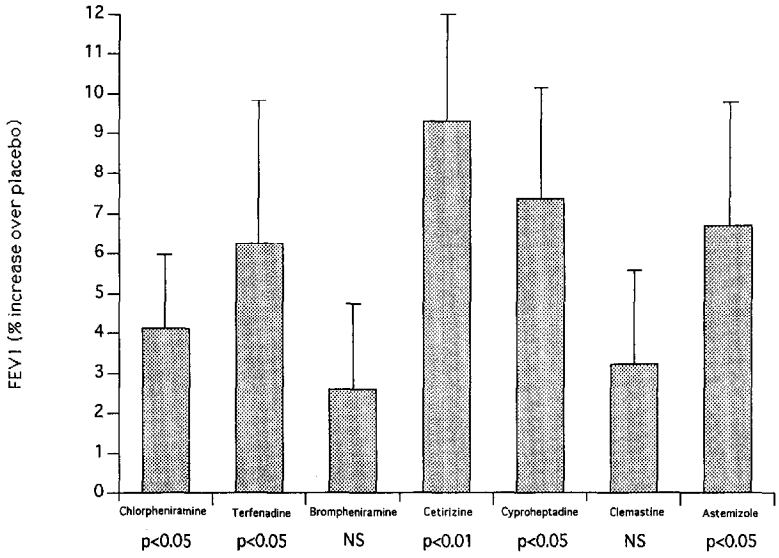

FIG. 1. The bronchodilator action of H_1-antihistamines expressed as the percentage increase in baseline FEV_1 after administration of active drug compared with that after administration of placebo. Each bar represents the mean ± SEM for 18 subjects.

were recorded at 10 minutes by transferring the wheal outline to transparent acetate sheets, which were stored until analysis.

Data analysis

The mean of the two baseline FEV_1 measurements on each study day was used to assess the effect of drug administration on initial airway caliber. Baseline FEV_1 measurements from the two study arms were combined and compared by Friedman's two-way analysis of variance (ANOVA) with subject and treatment variables. Differences between individual treatments were tested with a one-tailed Wilcoxon's rank-sum test. For the bronchial challenge results, the lower of the 1- and 3-minute FEV_1 measurements made at each agonist concentration was expressed as a percentage of the lowest FEV_1 after saline diluent administration. This was plotted against the cumulative concentration of agonist administered, expressed on a logarithmic scale. For each subject the log concentration-response curves after the various treatments were analyzed by the method of Fieller[22] to determine whether any of the responses departed significantly from parallel. For each treatment the provocation concentration of agonist required to cause a 20% fall in FEV_1 ($PC_{20}FEV_1$) was derived from the linear portion of the log concentration-response curve by interpolation. $PC_{20}FEV_1$ values were compared with Friedman's two-way ANOVA with subject and treatment variables. Differences between individual treatments were tested with a one-tailed Wilcoxon's rank-sum test. Any protective effect of an antihistamine compared with placebo against agonist-provoked bronchoconstriction was then expressed as a concentration ratio (i.e., $PC_{20}FEV_1$ after active treatment divided by $PC_{20}FEV_1$ value after placebo).

Skin wheal areas were measured by planimetry and plotted against the concentration of histamine expressed on a logarithmic scale. The slopes of the concentration-response curve were determined by linear regression, and these were compared by Friedman's two-way ANOVA with subject and treatment variables. Any difference between individual treatments was then assessed with Wilcoxon's rank-sum test. Any protective effect of active treatment compared with placebo was expressed as the slope of the concentration-response curve after active treatment divided by the slope of the concentration-response curve after placebo administration.

RESULTS

Baseline spirometry

Two subjects were withdrawn from the study because of deterioration of their asthma that required a change in their treatments, and analyses are thus restricted to nine subjects in each study arm. No study day baseline measurements of FEV_1 varied by more than 10%, nor was there a variation of more than 10% after inhalation of saline diluent. When compared with placebo, the mean baseline FEV_1 was higher after administration of all antihistamines. The increase in mean FEV_1 ranged from 2.58% after brompheniramine administration to 9.28% after cetirizine administration (Fig. 1). When baseline FEV_1 measurements were compared by means of Friedman's two-way ANOVA, there was a significant difference between treatments. With the exception of brompheniramine and clemastine, effects of all active treatments were significantly different from

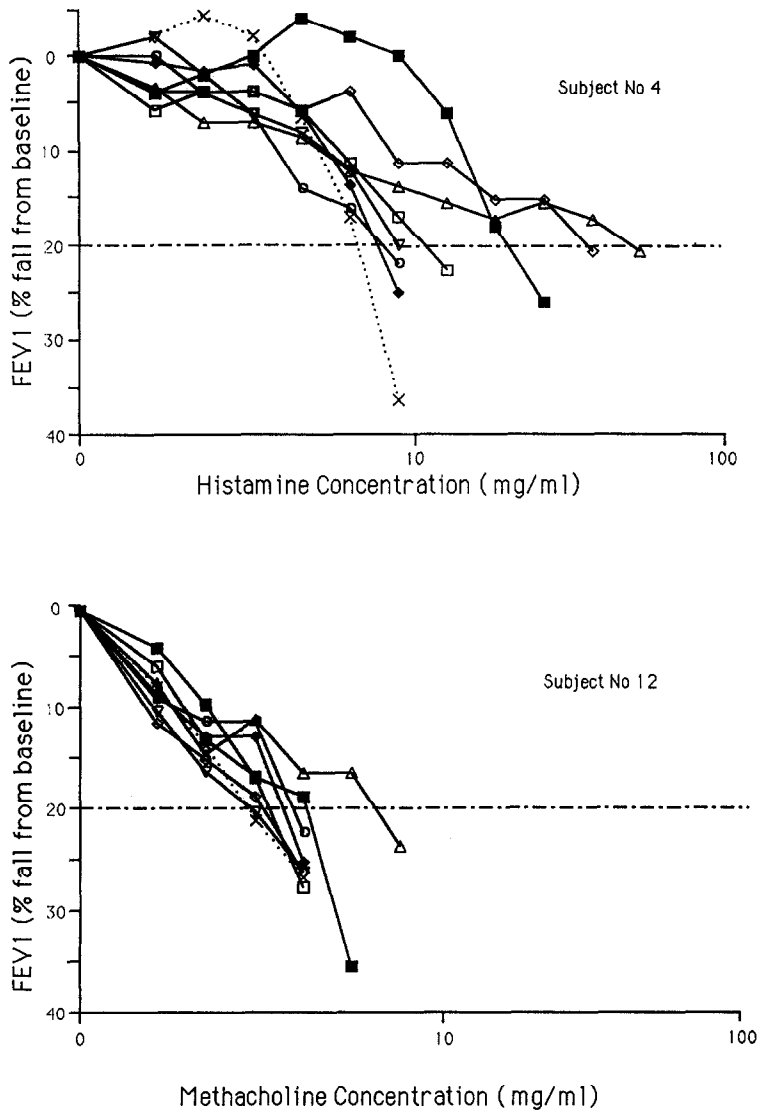

FIG. 2. Example of the effect of placebo and the different H_1-antihistamines on the FEV_1 response to inhaled histamine *(top)* and methacholine *(bottom)* in a single subject with asthma: placebo (X..X), chlorpheniramine (■-■), terfenadine (◇-◇), brompheniramine (O-O), cetirizine (△-△), cyproheptadine (▽-▽), clemastine (□-□), or astemizole (◆-◆).

those of placebo. In addition, baseline measurements after cetirizine administration were significantly different from those for chlorpheniramine ($p = 0.014$), brompheniramine ($p = 0.002$), and clemastine ($p = 0.001$). There was no correlation between the antihistamine-induced increase in FEV_1 and the percent predicted FEV_1 at enrollment.

Histamine-induced bronchoconstriction

After oral administration of placebo, inhaled histamine caused a concentration-related fall in FEV_1 with a geometric mean $PC_{20}FEV_1$ of 0.41 mg/ml (range, 0.04 to 2.83 mg/ml). All seven antihistamine drugs studied displaced the histamine concentration-response curve to the right when compared with placebo (Fig. 2). On three occasions (twice with cetirizine and once with terfenadine) the drug afforded such protection that a $PC_{20}FEV_1$ value could not be derived. On these occasions a value of 64 mg/ml, which represents 1 doubling dilution beyond the highest concentration administered, was assigned for analysis. In the remaining subjects the concentration-response curves did not depart significantly from parallel. When the $PC_{20}FEV_1$ values were analyzed by Friedman's two-way ANOVA, there was a significant difference between treatments

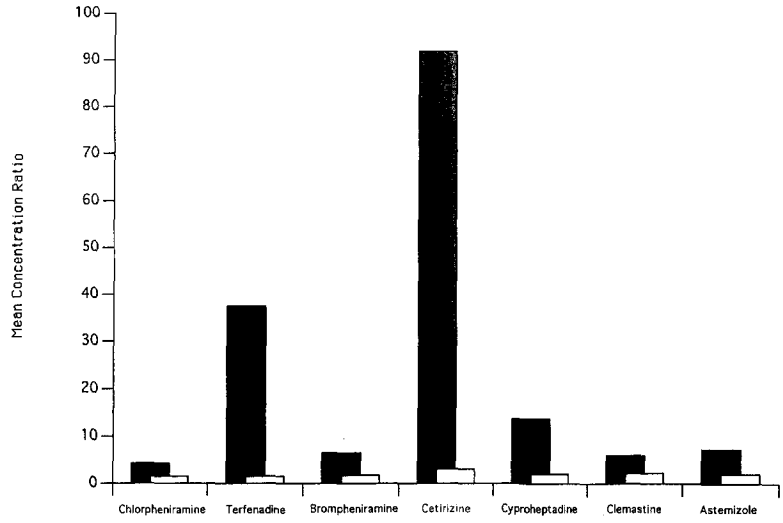

FIG. 3. The protective efficacy of antihistamines against the airway response to histamine *(shaded bars)* and methacholine *(open bars)* expressed as a mean concentration ratio for the nine subjects who completed the protocol for each inhalation challenge.

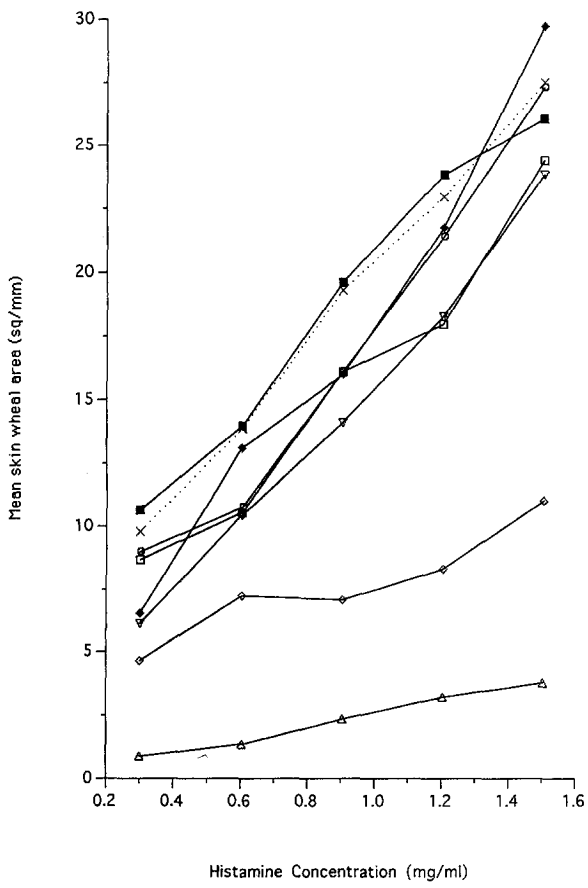

FIG. 4. Example of the effect of placebo and the different H_1-antihistamines on the histamine-induced skin wheal response in subjects with asthma: placebo (X..X), chlorpheniramine (■-■), terfenadine (◇-◇), brompheniramine (O-O), cetirizine (△-△), cyproheptadine (▽-▽), clemastine (□-□), or astemizole (♦-♦).

($p < 0.001$). Between treatments comparisons showed effects of all antihistamines to be significantly different from those of placebo. Cetirizine and terfenadine had a significantly greater effect than the other antihistamines in displacing the concentration-response curves, with cetirizine affording greater protection than terfenadine ($p = 0.018$). For each subject, by dividing the $PC_{20}FEV_1$ value after each antihistamine by that after placebo, we were able to calculate a concentration ratio for each drug. The relative protection afforded by each antihistamine is indicated by the mean concentration ratio, although for terfenadine and cetirizine this value will be a minimum estimate because of inclusion of censored data. We are thus able to rank the antihistamines according to their efficacy in relation to histamine-induced bronchoconstriction (Fig. 3).

Methacholine-induced bronchoconstriction

Methacholine caused a concentration related fall in FEV_1 after oral administration of placebo with a geometric mean $PC_{20}FEV_1$ of 0.32 mg/ml (range, 0.14 to 0.83 mg/ml). After administration of each of the seven antihistamines, the concentration-response curves to inhaled methacholine did not depart significantly from parallel (Fig. 2). $PC_{20}FEV_1$ values could be calculated for all subjects after all treatments, and none of the antihistamine drugs produced a change in $PC_{20}FEV_1$ values that was significantly different from that observed after placebo administration ($p = 0.18$).

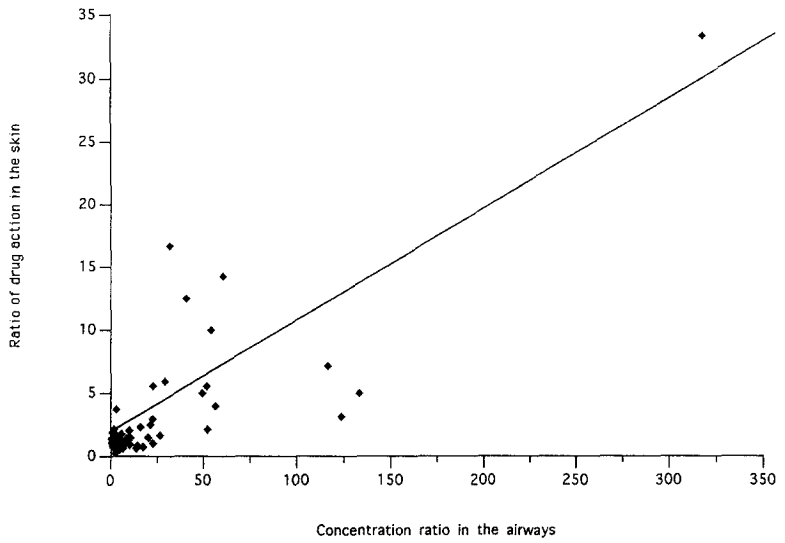

FIG. 5. The correlation between the antihistamine effect in the skin and airways of subjects with asthma ($r = 0.85$; $p < 0.01$).

The relative effect of each drug compared with that of placebo is indicated by the mean concentration ratio (Fig. 3).

Histamine-induced skin wheal

After placebo administration, histamine skin prick testing caused a wheal and flare reaction in all subjects, but only the wheal response has been subjected to analysis. The mean wheal area after placebo administration was 9.78 mm^2 (range, 2 to 20 mm^2) at 2 mg/ml, 14.11 mm^2 (range, 3 to 31 mm^2) at 4 mg/ml, 19.33 mm^2 (range, 10 to 27 mm^2) at 8 mg/ml, 23.00 mm^2 (range, 14 to 43 mm^2) at 16 mg/ml, and 27.56 mm^2 (range, 19 to 44 mm^2) at 32 mg/ml. After antihistamine pretreatment, any protective effect was shown by a downward displacement of the concentration-response curve (Fig. 4). Comparison of the slopes of the concentration-response curves by Friedman's two-way ANOVA showed a significant difference between treatments ($p < 0.0001$). The active treatments had a variable effect on histamine-induced skin wheal; many of the drugs demonstrated little if any suppression. Indeed, between treatments analysis with Wilcoxon's rank-sum test showed only terfenadine and cetirizine to be significantly different from placebo ($p = 0.004$) and these were also significantly different from the other antihistamines. In addition, the effect of cetirizine was significantly greater than that of terfenadine ($p = 0.005$). By calculating a ratio of the slope of the concentration-response curve in the skin for each active treatment compared with that for placebo, a comparison between the protective effect of the drugs in skin and airways was possible. When tested by linear regression the seven antihistamines demonstrated a close correlation ($r = 0.85$; $p < 0.01$) between their action in skin and airways as compared with placebo (Fig. 5).

Adverse effects

On arrival in the department, subjects were questioned regarding adverse effects with specific reference to sedation. Adverse effects were reported after all treatments, including placebo, with sedation ranging from 6% after cetirizine administration to 56% after cyproheptadine administration. The only adverse effects reported were sedation and dry mouth (Fig. 6), which were short-lived with resolution by the next day.

DISCUSSION

The main aim of this study was to compare older antihistamines with more recently developed drugs in a single group of subjects with asthma. In addition, we assessed the adverse effect profile of each drug, with particular reference to the anticholinergic activity in the airways as measured by their effect on methacholine-induced bronchoconstriction. Lastly we compared relative H_1-receptor antagonism in the skin and airways. The choice of antihistamines included in this study was determined by those commonly prescribed and available in the United Kingdom at the time of the study inception. Although we attempted to limit drugs to those with pure H_1-

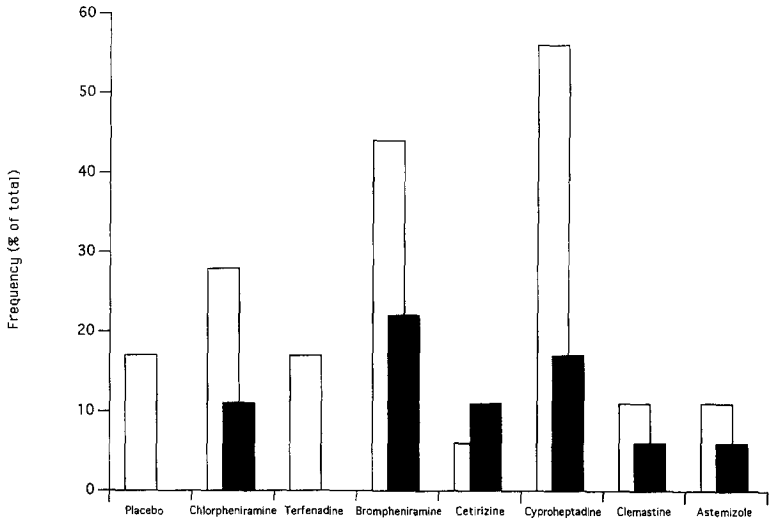

FIG. 6. The frequency distribution of drowsiness *(open bars)* and dry mouth *(shaded bars)* after a single oral dose of each of the H_1-antihistamines.

receptor actions, cyproheptadine was included as a positive control for its recognized antiserotonin actions and high incidence of adverse effects. The variable dosing regimens, coupled with differences in pharmacokinetic and pharmacodynamic profiles of the drugs, made the study design difficult; and as the best alternative to a double-blind randomized design, we conducted the study in a single-blind manner. Doses were guided by manufacturer's recommendations, which for older agents may reflect dose limitations imposed by adverse effects such as sedation. Although newer antihistamines do not appear to be limited by adverse effects, being devoid of central neurologic effects,[23, 24] the reasons behind dosage recommendations by manufacturers are unclear, particularly because some have shown increased H_1-receptor blockade at higher doses in vivo.[13] Unfortunately, the comparative potency of antihistamines, when expressed with doses of drugs at similar positions on their dose-response curves, has yet to be established in human beings, and the variability from animal experiments makes extrapolation to human beings unreliable.[25] A comparison on the basis of drug potency could not be performed with current information. Thus in an attempt to provide some relevance to clinical practice, we opted to use the manufacturer's recommended dose at a single time point and predose the subjects to allow peak plasma concentrations of the drugs to be achieved before bronchial challenge was undertaken.

When compared with placebo, antihistamine pretreatment caused bronchodilatation, and since this effect occurred to a variable degree with all active treatments, including those with no putative anticholinergic activity, one explanation for this effect would be the antagonism of endogenous histamine. The finding that the drug order for bronchodilator effect was similar to that for antagonism of exogenously administered histamine, both in the airways and skin, provides support for the concept that exogenous histamine contributes to airway tone in asthma. Although it is possible that the bronchodilator action is related to an alternative drug effect, further support for the role of histamine is found in the increased concentrations of histamine in bronchoalveolar fluid from subjects with asthma.[26, 27] In asthma the correlation between mast cell numbers and cell-free histamine in bronchoalveolar lavage,[28] together with an increase in the maximal histamine release from these cells in vitro,[29] point to mast cells as being the source of the histamine. We were unable to demonstrate any relationship between this effect on resting bronchomotor tone and starting airway caliber previously reported by other investigators.[4, 30]

The ability to construct reliable concentration-response curves with inhaled bronchoconstrictor agents in patients with asthma has allowed the action of receptor antagonists to be assessed more accurately in the airways. Although this approach has been used previously to describe the effects of a range of drugs in asthmatic airways (including terfenadine,[13] azelastine,[31] loratadine,[32] and ebastine[33]), to our knowledge this is the first time that this technique has been used to allow direct

comparison between different antihistamines in the same subjects. This has also enabled a rigorous study of the action of some of the older preparations in asthmatic airways. Thus although all the antihistamines that we studied provided some degree of protection against the constrictor effects of histamine, when compared with older preparations the new drugs were 5 to 15 times more effective at the doses used, a feature also observed for their H_1-blocking effects in the skin. Our results are in keeping with those of other investigators who have compared the suppressive effect of antihistamines in the skin of normal subjects.[34] The correlation between the protective effect of the antihistamines in the skin and airways suggests that the drugs have similar access to H_1-receptors that mediate the effects of histamine at both sites.

Although many of the older "less selective" drugs were associated with appreciable systemic adverse effects, an anticholinergic effect on the airways was not shown. However, since these drugs had high adverse effect profiles, although a dose increase may have improved airway protection against histamine, it would also certainly have resulted in an unacceptable incidence of adverse effects. These results demonstrate the clear advantages of the newer H_1-antihistamines as therapeutic agents in diseases in which histamine may be an important mediator. Indeed, there is recent evidence that both terfenadine[35] and cetirizine[36] exert a beneficial effect on allergic asthma during the pollen season. Although it is likely that this results from their powerful H_1-receptor antagonism, both have been shown to have other actions that may contribute to their effect in asthma, including inhibition of cell mediator release[37, 38] and eosinophil recruitment in the skin.[39]

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