A study of the clinical efficacy of azelastine in patients with extrinsic asthma, and its effect on airway responsiveness

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1 The effect of 4.4 mg azelastine administered orally on airway responsiveness, skin prick testing, daily peak expiratory flow rates and symptoms of asthma was compared with placebo in a 7 week double-blind, parallel group study of 24 patients with extrinsic asthma. The study was in two parts: a 2 week assessment period, during which all patients received placebo tablets but recorded daily peak flow rates (PEFRs) and symptoms, preceding the 7 week double-blind comparison.

2 Azelastine, 4.4 mg, significantly decreased airway responsiveness to histamine compared with placebo both after a single dose ($P < 0.001$), and following 7 weeks continuous treatment ($P < 0.02$). Airway responsiveness to methacholine was not altered by administration of azelastine compared with placebo.

3 Skin prick test weal diameters to both allergen and histamine were significantly reduced after both a single dose and following 7 weeks continuous therapy treatment with azelastine.

4 There was a significant improvement in both the mean of the morning and the evening peak flow rates recorded during the last week compared with the first week of the study in the group receiving 4.4 mg of azelastine twice daily compared with placebo. Scores for wheeze were significantly reduced during the final 3 weeks of the study in patients receiving azelastine compared both with those receiving placebo and with the first week of the study ($P < 0.05$, $P < 0.01$). Consumption of inhaled bronchodilators fell significantly during the study in the group receiving azelastine therapy ($P < 0.05$); no such fall occurred in the placebo treated patients.

5 A bitter metallic taste was reported by 58% of patients who received azelastine therapy.

Keywords azelastine asthma airway responsiveness H₁-receptor antagonist

Introduction

Azelastine, 4-(*p*-chlorobenzyl)-2-(hexahydro-1-methyl-1H-azepin-4-yl)-1(2H)-phthalazinone hydrochloride is a recently introduced, orally active, compound with potent H₁-receptor blocking activity but negligible anti-cholinergic effects (Diamantis *et al.*, 1981; Katayama *et al.*, 1981; Mandi *et al.*, 1981; Zechel *et al.*, 1981). In addition to its H₁-receptor antagonism, azelastine has been shown to inhibit the release of histamine

from mast cells *in vitro* by both allergic stimuli (Chand *et al.*, 1983b) and by non-immunologic secretagogues, including compound 48/80, Concanavalin A (Fields *et al.*, 1981) and calcium ionophore (Chand *et al.*, 1983c). More recently Little *et al.* (1987) have shown that azelastine inhibits anti-IgE induced human lung mast cell degranulation in a dose-dependent manner. Diamantis *et al.* (1984) have also demonstrated

that azelastine exerts a potent, dose-dependent and long lasting inhibitory effect *in vivo* on passive cutaneous anaphylaxis (PCA) in the rat.

In addition to its inhibitory effects on both the release and action of histamine, azelastine has also been shown to inhibit the *in vitro* release of leukotrienes from rat peritoneal mast cells in response to calcium ionophore. Azelastine also antagonises the action of leukotrienes in causing contractions in isolated guinea pig ileum (Diamantis *et al.*, 1982). Furthermore *in vivo* studies by Chand *et al.* (1983a) have demonstrated that azelastine exerts a long-lasting effect on leukotriene mediated bronchoconstriction in the anaesthetised guinea pig superior to that of aminophylline, ketotifen and sodium cromoglycate.

There have been few *in vivo* studies of the effect of azelastine in man. However, Albazzaz & Patel (1987) have recently reported that azelastine does not appear to block the effects of inhaled LTC₄ in humans despite a significant inhibition of the effects of histamine inhalation in the same individuals. We have previously reported the attenuation of the immediate asthmatic response to allergen inhalation in man following 21 days treatment with azelastine 4.4 mg twice daily (Ollier *et al.*, 1986). However, although a drug may diminish the bronchial response to an allergen on provocation testing it may not be effective clinically (Muittari *et al.*, 1978). In contrast it has been demonstrated that the degree of airway responsiveness to pharmacological agents such as histamine and methacholine relates both to the overall severity of asthma symptoms (Makino, 1966; Murray *et al.*, 1981) and the amount of treatment required (Juniper *et al.*, 1981) and recent studies have suggested that drugs useful in the management of asthma may lessen the degree of airway responsiveness (Rocchiccioli *et al.*, 1984; Hartley, 1984).

The aim of the present study was therefore to assess the clinical efficacy of azelastine in man and investigate its effect on airway responsiveness to methacholine.

Methods

Patients

Twenty-four patients, five female and 19 male, with an age range of 18–45 years (mean age 23.4 years), with extrinsic allergic asthma were studied. The mean duration of their asthma symptoms was 11.7 years. All were atopic, in that they had one or more wealing reactions of crossed diameters ≥ 3 by 3 mm 15 min after skin prick

testing with *Dermatophagoides pteronyssinus*, 1.2% weight/volume (w/v); house dust, 150% w/v; *Aspergillus fumigatus*, 5% w/v and mixed grass pollens, 2.5% w/v (Bencard, Brentford, UK). All patients exhibited reversible airflow limitation with an increase of $\geq 15\%$ in the forced expiratory volume in one second (FEV₁) 15 min after inhalation of 200 µg salbutamol.

On entry to the study all patients were taking oral or inhaled salbutamol or terbutaline. None had received treatment with inhaled or oral corticosteroids, sodium cromoglycate or theophylline derivatives in the 3 weeks prior to the study. Throughout the course of the study patients were allowed only symptomatic medication in the form of inhaled bronchodilator therapy.

Each patient gave written informed consent to participation in the study and the project was approved by the Hospital Ethics Committee. Patients were withdrawn from the study if they developed an upper or lower respiratory tract infection or experienced unacceptable unwanted effects during the course of the study. The study was performed between the months of November and May in order to avoid the grass pollen season.

Study design

Administration of drugs and placebo The effect of 4.4 mg of azelastine on respiratory function, symptoms, salbutamol usage, airway responsiveness to methacholine and histamine and the skin wealing response to allergen and histamine was compared with that of placebo in a randomised, double-blind, parallel group study. Part 1 of the study consisted of a 2 week single-blind run in period during which all patients received placebo tablets twice daily. During Part 2 of the study patients were randomly allocated to receive continuous therapy with 4.4 mg azelastine twice daily or with identical placebo tablets for 7 weeks in a double-blind fashion (study therapy).

Compliance Patient compliance with therapy was estimated by tablet counts of study medication returned. All medications issued contained a randomised excess of tablets to ensure that the investigators were blind to the degree of compliance of each patient during the course of the study.

Respiratory function tests A whole body plethysmograph (Gould 2800 Autobox, Gould Medical Ltd, Coventry, UK) was used to measure forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), residual volume

(RV), peak expiratory flow rate (PEFR), maximal mid-expiratory flow rate (MMEF), total lung capacity (TLC), total intra-thoracic gas volume (TGV), airways resistance (Raw), and specific airways conductance (sGaw). These tests were performed at the start of the run in period, on entry to the double-blind study, and at the end of 6 weeks continuous treatment. On each occasion respiratory function was measured prior to the morning dose of azelastine or placebo. At every attendance repeat measurements of sGaw were obtained 4 h after administration of azelastine or placebo, at time at which peak plasma levels of azelastine could be expected as described by Spector *et al.* (1987).

Airway responsiveness Airway responsiveness was assessed by inhalation of both histamine acid phosphate and methacholine chloride (Sigma Chemical Company Ltd, Poole, Dorset, UK). Both agonists were diluted using phenol saline (0.4% phenol, 0.275% sodium bicarbonate in 0.5% sodium chloride) to provide doubling concentrations from 0.03–8.0 mg ml⁻¹. Provocation tests were performed according to the tidal breathing method recommended by Cockcroft *et al.* (1977) adapted by the use of a De Vilbiss 646 nebuliser (De Vilbiss Health Care UK Ltd, Feltham, Middx, UK). Control solution (phenol saline) and increasing concentrations of agonist were inhaled during 2 min of tidal breathing at a flow rate of 7 l min⁻¹. Airway response to provocation was measured in terms of sGaw immediately before and 5 min after inhalation of control solution and each subsequent concentration of methacholine or histamine. Inhalation of either agonist was terminated when a $\geq 35\%$ fall in sGaw from the lowest value recorded following inhalation of the control solution was recorded. A dose-response curve was constructed for each provocation test by plotting the non-cumulative concentration of agonist logarithmically on the abscissa against sGaw as a percentage of the control value on the ordinate. The provocation concentration resulting in a 35% fall in sGaw was determined and recorded as the PC₃₅-sGaw. When a fall of 35% or more in sGaw had been obtained patients were asked to inhale 200 µg of salbutamol to relieve any continuing air-flow limitation.

Provocation testing with both methacholine and histamine was carried out after single administration of azelastine or placebo during Part 1 of the study and during Part 2 of the study after 6 or 7 weeks continuous therapy respectively. Responsiveness to methacholine and histamine were performed on separate days, 1 week apart. Testing was in a set order with methacholine

first, on days 8 and 57, followed by histamine on days 15 and 64. All tests were performed at the same time of day and, when preceded by administration of study therapy, were performed 4 h after dosing.

Skin prick testing Skin prick testing with common inhalant allergens (*D. pteronyssinus*, housedust, mixed grass pollens and *Aspergillus fumigatus*), a negative control solution (isotonic saline) and a positive control solution (histamine acid phosphate 10 mg ml⁻¹) was performed on entry to the study. For each individual the allergen which elicited the largest skin weal during this initial screening was used in all subsequent tests.

Skin prick testing was repeated following a single administration of azelastine or placebo during Part 1 of the study and again after six weeks continuous therapy in Part 2 of the study. On each occasion testing was performed in duplicate on the volar surface of the forearm with four concentrations of the appropriate allergen (1:500, 1:1000, 1:5000, 1:10,000 weight/volume) and three concentrations of histamine (2.5, 5 and 10 mg ml⁻¹) 4 h after dosing with study therapy. Weal outlines were traced 12 min after testing using a ballpoint pen, transferred to graph paper using adhesive tape and areas recorded in mm².

Daily symptoms, peak expiratory flow rates and consumption of bronchodilator therapy Patients were asked to record three measurements of PEFR twice daily, on waking and before retiring, using a 'Mini-Wright' portable peak flow meter (Clement Clarke International, London, UK) prior to inhaling bronchodilator medication. Patients were also asked to record subjective assessments of cough severity, breathlessness, wheeze, limitation of activity due to asthma, and sleep disturbance in a diary card daily. Severity was scored on a four point scale where 1 = none, 2 = mild, 3 = moderate and 4 = severe. In addition to severity of symptoms the number of actuations of the salbutamol metered dose inhaler were recorded daily. Consumption of inhaled bronchodilators was determined by weighing canisters at each visit.

Toxicological studies A sample of venous blood (15 ml), for testing of haematological, hepatic, and renal function, a mid stream urine sample and an electrocardiogram were obtained on entry to and at the end of the study. Haematological tests performed included measurements of haemoglobin, red cell count, packed cell volume, white cell count, and platelet count. Chemical

analyses included measurements of urea, creatinine, uric acid, bilirubin, alkaline phosphatase, specific glutamic oxaloacetate transferase, gamma glutamyl transpeptidase and glucose. Urine analyses included recordings of pH, protein, glucose, and blood.

Unwanted effects At each attendance the patients' response to a 'non-leading' question about possible unwanted effects of therapy was documented.

Statistical analyses

Parametric or non-parametric tests were applied according to the nature of the data being examined. Changes from baseline were examined within each treatment group using analysis of variance followed by paired Student's *t*-tests or Friedman's analysis of variance followed by Wilcoxon's signed rank pairs test as appropriate. Comparisons between groups were performed using unpaired *t*-tests or Mann-Whitney 'U' tests as appropriate. Where appreciable differences occurred between groups prior to treatment variables were examined with respect to changes from untreated levels. A significance level of $P < 0.05$ (two-tailed) was adopted throughout the analysis for rejection of the null hypothesis.

Results

Details of patient characteristics are displayed in Table 1. There were no statistically significant differences between the two treatment groups in respect of sex distribution, FEV₁ (% predicted), resting respiratory function, bronchial responsiveness to inhaled histamine or previous drug therapy. There was a statistically significant difference in mean age between the two groups; the mean age of the placebo treated group being 21.25 years and the azelastine treated group being 25.5 years. There were no differences between the treatment groups in terms of the mean weal areas in response to skin prick testing with control solution, housedust, housedust mite (*D. pteronyssinus*), mixed grass pollens, *Aspergillus fumigatus* or histamine acid phosphate 10 mg ml⁻¹. Three patients were withdrawn from the study; two placebo treated patients were withdrawn on day 15 as a result of non-attendance and poor co-operation, and one azelastine treated patient was withdrawn on day 8 due to nausea following a single dose of azelastine 4.4 mg.

Compliance

Compliance with therapy was good with the majority of patients (16/21) taking over 90% of

Table 1 Patient characteristics on entry to the study

Patient	Age (years)	Sex	FEV ₁ (l)	% predicted	Duration of asthma (years)	Treatment allocated
1	22	M	4.1	102	5	A
2	22	M	4.1	91	17	P
3	21	M	3.3	75	16	P
4	23	M	4.5	107	19	A
5	22	M	4.4	96	18	A
6	21	M	5.2	109	14	P
7	22	M	4.7	101	3	A
8	34	M	5.6	136	10	A
9	24	M	3.0	66	0.75	P
10	22	M	4.4	99	2.5	P
11	21	M	5.0	107	2	A
12	18	F	2.6	75	18	P
13	22	M	5.4	121	4	A
14	21	M	3.4	76	10	P
15	21	M	5.2	118	1	P
16	33	M	3.9	94	17	A
17	25	F	2.9	91	10	A
18	22	M	4.7	111	10	P
19	21	M	4.5	98	21	A
20	38	M	3.7	94	4	A
21	21	M	4.0	104	16	P
22	23	F	2.6	85	23	A
23	20	F	3.6	109	17	P
24	22	F	3.7	118	22	P

A = Azelastine 4.4 mg, P = placebo.

the treatment prescribed, on the basis of return tablet counts.

Respiratory function tests

None of the variables measured on arrival in the laboratory (between 08.00 and 10.00 h) showed any significant changes on any occasion during treatment with either 4.4 mg azelastine or placebo. However, changes in airflow limitation, as measured by sGaw, were observed 4 h after dosing with azelastine (Figure 1). These changes were significant only after administration of a single dose of azelastine ($P < 0.05$, $P < 0.05$; Wilcoxon signed rank pairs test) and not during continuous treatment. Small, but insignificant, rises in sGaw also occurred in placebo treated patients 4 h after dosing. When the treatment groups were directly compared bronchodilatation resulting from azelastine was significantly greater than with placebo when given as a single dose during the run in period ($P < 0.02$).

Figure 1 Changes in airflow limitation before (□) and 4 h after (■) dosing with 4.4 mg of azelastine.

Airway responsiveness

In several individuals pre-treatment with azelastine resulted in complete protection from bronchoconstriction even at the highest concentrations of histamine available. For this reason analyses of the results of bronchial provocation tests were performed on ranked data, and group results expressed as median concentrations of histamine or methacholine required to produce a 35% fall in sGaw. The median PC₃₅ sGaw for methacholine was slightly higher in the azelastine treated group after both a single administration and after 6 weeks treatment when compared with the group receiving placebo medication. However, this difference did not reach statistical significance (Figure 2). In contrast, after both a single administration of azelastine and after 6 weeks treatment the PC₃₅ sGaw for histamine was significantly higher than after administration of placebo ($P < 0.001$, $P < 0.02$ respectively;

Figure 2 Median values of PC₃₅-sGaw following administration of single or multiple doses of placebo (□) or azelastine 4.4 mg (■).

Table 2 Individual values of PC₃₅ sGaw (mg ml⁻¹) following administration of single or multiple doses of placebo or azelastine

Patient	Placebo		Patient	Azelastine 4.4 mg	
	Single dose	Continuous therapy		Single dose	Continuous therapy
2	0.098	0.046	1	4.170	7.800
3	0.105	—	4	4.300	8.600
6	0.420	0.390	5	0.125	0.074
9	0.160	0.012	7	2.700	0.017
12	0.159	0.098	8	CP	184.000
14	0.110	0.150	11	2.700	2.150
15	0.820	1.400	13	2.500	8.400
21	0.300	0.080	16	0.215	1.580
23	0.088	0.014	17	25.000	0.700
24	0.040	0.220	20	0.690	48.000
			22	0.335	0.041
Median value	0.159	0.098		2.63*	2.15**

* $P < 0.001$ compared with placebo (Mann Whitney U test).

** $P < 0.02$ compared with placebo (Mann Whitney U test).

(CP) indicates complete protection from the effects of histamine inhalation even at the highest concentration available (32 mg ml⁻¹)

(—) indicates a missing value for patient 3 who was excluded from the analysis.

Table 3 Mean weal areas in response to skin prick testing with allergen and histamine during continuous treatment with azelastine or placebo

	Mean weal area (mm ²)		P-value (Mann Whitney U test)
	Placebo	Azelastine	
<i>[Allergen] w/v</i>			
1:500	26.01 ± 8.22	10.05 ± 2.75	< 0.01
1:1000	19.80 ± 3.28	7.50 ± 2.01	< 0.01
1:5000	8.95 ± 2.09	3.55 ± 0.72	< 0.02
1:10,000	7.55 ± 1.42	2.18 ± 0.46	< 0.01
<i>[Histamine] mg ml⁻¹</i>			
10.0	11.1 ± 1.8	4.4 ± 1.1	< 0.01
5.0	11.5 ± 2.8	3.5 ± 0.5	< 0.002
2.5	9.6 ± 1.5	3.3 ± 0.8	< 0.002

Mann Whitney 'U' test). The results of histamine provocation tests for each individual patient are displayed in Table 2.

Skin prick testing

A significant reduction in the mean weal area in response to only the most concentrated solution of allergen (1:500) occurred 4 h after a single administration of 4.4 mg azelastine compared with placebo.

However, after 6 weeks treatment a single administration of azelastine 4.4 mg produced a significant reduction in the skin wealing response

for all the dilutions of allergen compared with placebo (Table 3). Comparable results occurred after skin prick testing with histamine, weal size being significantly reduced only in the highest histamine concentration after a single administration of azelastine during the run in period but for all dilutions after 6 weeks treatment compared with placebo.

Daily symptoms, peak expiratory flow rates and salbutamol usage

Mean daily morning and evening PEFs were calculated for each week of the study period and

Table 4 Mean daily PEFRs, from patient diaries, during treatment with placebo or azelastine. a) shows mean morning PEFRs. b) shows mean evening PEFRs

<i>b</i>											
Mean morning PEFR (l min ⁻¹)										Mean evening PEFR (l min ⁻¹)	
Patient	1	2	3	4	5	6	7	8	9	Week	
<i>Placebo</i>											
2	553.5	550.8	545.0	549.3	559.3	545.0	534.3	525.0	545.0	545.0	2
3	445.7	441.7	401.4	348.6	382.9	407.1	412.9	406.7	396.7	396.7	3
6	658.3	681.4	665.0	664.3	667.1	665.7	640.0	628.3	615.0	615.0	6
9	491.7	485.2	485.2	530.0	562.9	533.8	526.2	479.0	481.0	481.0	9
12	397.5	386.7	391.4	382.9	390.0	385.7	372.9	395.7	392.9	392.9	12
14	532.4	541.4	498.6	521.0	489.0	523.3	497.6	472.4	481.1	481.1	14
15	501.7	525.7	555.7	557.1	544.3	545.7	560.0	547.1	—	—	15
21	528.3	525.7	498.6	510.0	507.0	527.1	517.1	541.4	537.1	537.1	21
23	416.6	417.1	386.7	390.0	372.9	391.4	372.9	371.4	380.0	380.0	23
24	505.7	478.6	504.3	507.1	488.6	480.0	494.3	501.4	486.7	486.7	24
PEFR Mean	503.3	501.1	486.2	489.2	491.1	495.5	485.5	480.1	479.5	479.5	PEFR Mean
Δ PEFR Mean	—	-2.3	-17.1	-14.1	-12.1	-7.8	-17.8	-23.2	-23.8	-23.8	Δ PEFR Mean
<i>Azelastine</i>											
1	557.5	562.9	545.7	552.9	544.3	545.7	541.4	550.0	561.4	561.4	1
4	482.9	480.7	468.3	511.4	512.9	527.1	527.1	531.4	520.0	520.0	4
5	623.3	632.9	628.3	628.6	612.9	620.0	—	—	—	—	5
7	590.0	595.7	569.5	581.0	577.6	582.9	579.0	580.0	595.7	595.7	7
8	665.4	704.8	696.2	708.9	727.8	722.1	671.0	705.7	699.3	699.3	8
11	582.1	588.6	617.1	615.7	607.9	598.6	597.9	610.0	598.3	598.3	11
13	588.6	564.8	526.2	540.0	512.3	567.4	546.4	547.6	590.8	590.8	13
16	520.0	507.1	527.1	517.1	520.0	508.6	547.1	522.9	531.4	531.4	16
17	391.7	391.4	384.3	388.6	387.1	391.4	392.9	392.9	396.7	396.7	17
20	408.9	432.9	425.6	402.4	421.0	407.1	407.6	422.4	423.8	423.8	20
22	412.1	395.0	448.3	433.6	471.4	388.6	377.1	383.6	399.2	399.2	22
PEFR Mean	519.9	522.4	520.8	525.2	528.2	524.0	518.8	524.7	531.7	531.7	PEFR Mean
Δ PEFR Mean	—	+2.5	+0.9	+5.3	+8.3	+4.1	-1.1	+4.8	+11.8*	+11.8*	Δ PEFR Mean

(—) denotes missing values (patients with incomplete records were excluded from statistical analysis).
 *absolute change from pre-treatment levels significantly different from placebo-treated patients ($P < 0.01$).

are shown in Table 4 (a and b). Throughout the study there was no significant difference between morning and evening peak flow recordings. No significant change in either morning or evening PEFR was seen in either group until the final 2 weeks of the continuous treatment period when both morning and evening PEFR rose in the azelastine treated group compared with untreated baseline levels and fell in the placebo group. During the final week of treatment the absolute change from pre-treatment levels was significantly greater in the group treated with azelastine 4.4 mg than in the group treated with placebo ($P < 0.01$; unpaired t -test).

Severity of symptoms of cough, wheeze, breathlessness, activity limitation and sleep disturbance were expressed as mean scores for each week of the study period. No significant change occurred in the scores for cough, sleep disturbance, activity limitation or breathlessness throughout the study in either treatment group. However, scores for wheeze, shown in Table 5, fell progressively in patients treated with azelastine 4.4 mg, and were significantly lower (1.18) during the final week of the study than prior to treatment (1.56) ($P <$

0.05; paired t -test). During the last 3 weeks of the study wheeze scores in the group receiving active therapy were also significantly lower than in the placebo group.

There was a fall in mean weekly usage of bronchodilators, recorded daily in diary cards, in both treatment groups during the course of the study. Consumption fell by a greater amount in the azelastine treated patients and was significantly decreased from pre-treatment levels after 2, 4, 5 and 7 weeks therapy ($P < 0.05$ in each case). Canister weights fell by a greater amount in the placebo group than in the azelastine treated group but this difference did not reach significance.

Toxicological studies

Recordings of pulse and blood pressure at each visit showed no significant changes over the study period in either the patients receiving azelastine therapy or in the placebo treated patients. There was no significant difference in laboratory results of haematological, hepatic and renal function during the course of the study.

Table 5 Mean daily wheeze scores during treatment with placebo (upper table) or azelastine (lower table)

Patient	Mean daily wheeze score								
	1	2	3	4	Week 5	6	7	8	9
2	1.0	1.0	1.0	1.0	1.0	1.9	1.7	1.3	1.0
3	2.0	2.1	2.4	2.1	2.0	1.6	2.0	2.0	2.9
6	1.0	1.0	1.0	1.0	1.0	1.0	1.3	1.0	1.0
9	1.7	2.1	2.1	2.0	1.4	1.4	1.7	2.0	1.9
12	1.4	1.0	1.0	1.1	1.0	1.0	1.0	1.0	1.1
14	1.0	1.1	1.4	1.0	1.6	1.1	1.4	1.6	1.3
15	1.0	1.0	1.1	1.0	1.0	1.0	1.0	1.0	1.0
21	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
23	1.3	1.6	1.6	1.4	1.7	1.6	1.0	1.3	1.4
24	1.1	1.3	1.3	1.1	1.1	1.4	1.1	1.1	1.3
Mean	1.25	1.32	1.39	1.27	1.28	1.30	1.32	1.33	1.39
1	1.3	1.1	1.1	1.7	1.1	1.3	1.1	1.0	1.0
4	1.0	1.0	—	—	—	—	—	—	—
5	2.1	2.0	1.3	1.4	1.4	1.0	—	—	—
7	1.1	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
8	1.1	1.1	1.0	1.0	1.0	1.0	1.0	1.0	1.0
11	1.3	1.3	1.1	1.1	1.0	1.0	1.0	1.0	1.0
13	1.0	1.3	1.0	1.1	1.0	1.0	1.0	1.0	1.0
16	2.0	2.3	1.9	2.4	2.3	1.1	1.0	1.1	1.1
17	2.0	1.3	1.4	1.3	1.1	1.4	1.0	1.0	1.1
20	1.9	1.9	1.6	2.0	2.0	2.0	2.0	2.0	2.0
22	2.3	1.6	1.1	1.3	1.0	1.3	1.0	1.3	1.4
Mean	1.56	1.43	1.24	1.43	1.28	1.23	1.12*	1.16*	1.18*

* $P < 0.05$ compared with pre-treatment values (paired t -test).

(—) denotes missing values (patients with incomplete records were excluded from statistical analysis).

Unwanted effects

In response to a non-leading question about unwanted effects 58% (7/12) patients receiving azelastine therapy reported a 'bitter' or 'metallic' taste in the mouth which was exacerbated by cold drinks.

Discussion

In this study we have demonstrated that azelastine 4.4 mg administered orally significantly inhibits the effect of inhaled histamine following both a single dose and after 7 weeks' continuous twice daily therapy, findings in agreement with those of Albazzaz & Patel (1987). The inhibitory effect of azelastine on bronchial provocation testing with histamine confirms the known, potent antihistaminic activity of this compound as described by Zechel *et al.* (1981). In contrast, we were unable to show any effect of azelastine on the response to inhalation of methacholine. Since specific airways conductance immediately prior to provocation with histamine did not differ from that recorded prior to provocation testing with methacholine this difference could not be attributed to differences in initial airway geometry.

Azelastine therapy resulted in a fall in the mean weekly consumption of inhaled bronchodilators. Despite this reduction in concomitant medication, morning and evening PEFs were maintained in the group receiving active therapy compared with placebo treated patients where levels of PEFs showed significant falls during the study period. Symptom scores differed little between the treatment groups, possibly due to patients' varying usage of inhaled therapy. However, azelastine treated patients did record a decreased occurrence and severity of wheeze as the study progressed.

In this study we have shown an improvement in asthma symptoms during treatment with azelastine which was unrelated to changes in hyperresponsiveness to inhaled methacholine although large changes in airway responsiveness to histamine did occur. Antihistaminic compounds have, in the past, failed to be of significant benefit in the treatment of asthma (Karlin *et al.*, 1972). It has been suggested that the poor efficacy of H₁-antihistamines in asthma may be a result of their low potency as competitive antagonists when high local concentrations of histamine are released in the airways and insufficient drug concentrations at bronchial H₁-receptors to produce effective antagonism (Holgate *et al.*, 1985). The use of larger doses of early

antihistamines was limited by the anticholinergic and sedative side effects of these drugs. However, newer non-sedating antihistamines such as terfenadine (Sorkin & Heel, 1985) are now being used to assess the value of H₁-receptor blockade in asthma since higher doses can now be used without the occurrence of unwanted effects. Indeed Taytard *et al.* (1987) have recently shown terfenadine to be significantly more effective than placebo in reducing symptom scores and increasing peak expiratory flow rates in mild extrinsic asthma.

The same compound has been shown to attenuate the bronchoconstrictor response to allergen provocation by 50% in a dose which completely inhibited the response to inhaled histamine (Rafferty *et al.*, 1987). The results of both Taytard *et al.* (1987) and Rafferty *et al.* (1987) using terfenadine accord well with our own experience with azelastine. Further work is required to elucidate whether the clinical improvement which we recorded was solely attributable to the potent H₁-receptor antagonism of azelastine or to an additional 'anti-allergic' activity.

In the context of the present study one possibility which should be considered is that azelastine does affect airway responsiveness, but in a way which is not detected by the use of an inhaled parasympathomimetic such as methacholine. The factors which control airway responsiveness are still incompletely understood, but a number of theories have been suggested including a lowered threshold for stimulation in the vagal constrictive reflex arc from airway mucosa to airway smooth muscle (O'Byrne *et al.*, 1981). The vagal reflex could occur following stimulation of afferent bronchial irritant receptors and cause release of acetylcholine from terminal efferent nerve endings, activating muscarinic receptors and resulting in contraction of bronchial smooth muscle (Boushey *et al.*, 1980).

Methacholine produces its effect by activation of the post ganglionic muscarinic receptors in the airways (Koelle, 1966) thus testing the final portion of this reflex—the contraction of smooth muscle in response to stimulation of muscarinic receptors. If airway hyperresponsiveness is due in part to inflammatory reactions in the airways causing bronchial irritant receptors to be more easily stimulated a reduction in inflammation and subsequent diminution of the vagal reflex would be a possible mode of action for compounds such as corticosteroids (as suggested by Easton in 1981) or azelastine. In this case methacholine would not detect a change in responsiveness since it does not test the afferent portion of the vagal reflex.

It is possible that the action of azelastine in

reducing asthma symptoms could be explained in terms of an effect on inflammation of the airways. Some of the most potent mediators of this process are the leukotrienes, and azelastine has been shown to inhibit both the release and action of leukotrienes in animal models. However, Albazzaz & Patel (1987) have recently shown that azelastine does not attenuate the bronchoconstrictor response to inhaled leukotriene C₄ (LTC₄) in man though the effect of this drug on the release and action of other sulphido-peptides and chemoattractant leukotrienes is not known.

In conclusion, we have confirmed the antihistaminic activity of azelastine in man, since oral administration of this compound resulted in significant inhibition of both airflow limitation and the skin wealing response to histamine. We have also shown a reduction in both asthmatic symptoms and consumption of inhaled bronchodilators during long term treatment with aze-

lastine. We found orally administered azelastine to be generally well tolerated, the only unwanted effect being a bitter taste in the mouth which persisted during treatment. These findings suggest that azelastine may be a safe and effective oral treatment in extrinsic asthmatic patients. Since the clinical benefits of azelastine therapy were not associated with a decrease in airway responsiveness to methacholine, further work is required to elucidate the mode of action of this drug in man.

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