

A comparison of the effects of oral cetirizine and inhaled beclomethasone on early and late asthmatic responses to allergen and the associated increase in airways hyperresponsiveness

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Summary

Background Cetirizine is a non-sedating H₁ antihistamine which is effective in the treatment of allergic rhinitis and urticaria. It inhibits eosinophil and basophil chemotaxis in late cutaneous allergic reactions in skin windows. Its effect on early (EAR) and late asthmatic reactions (LAR) is less certain.

Methods We examined the effect on EAR and LAR of 3 days treatment with oral cetirizine (15 mg twice daily) compared with a single dose of inhaled beclomethasone 10 min prior to allergen challenge in a placebo-controlled (oral and inhaled) double-blind cross-over design with three treatment arms separated by 14 days.

Results Cetirizine did not significantly inhibit either the EAR or LAR documented by maximum percentage fall in FEV₁ (0–3 and 6–9 h) or as area under the curve (AUC between 0 and 3 and 6–9 h). Beclomethasone inhibited the LAR compared with placebo ($P=0.02$) when expressed as AUC (6–9 h). This did not quite reach statistical significance ($P=0.06$) when expressed as maximal percentage late fall in FEV₁ between 6 and 9 h. A greater than twofold increase in airways responsiveness to methacholine was observed 3 h after challenge which was significantly reduced by beclomethasone compared with placebo ($P<0.02$) and cetirizine ($P<0.05$). The data suggest that oral cetirizine does not significantly inhibit either the EAR or LAR. Beclomethasone inhibited both the early increase in airways responsiveness and the subsequent LAR. Our study also confirms the view that early increases in airway responsiveness precede the late response and suggests that these associated events are not dissociable by the pharmacological treatments employed in this study.

Keywords: allergen inhalation challenge, beclomethasone, cetirizine, early asthmatic reaction, late asthmatic reaction

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Introduction

Cetirizine (the principal metabolite of hydroxyzine) is a second generation non-sedating highly selective H₁

antihistamine which is effective in the treatment of allergic rhinitis and urticaria [1–6]. The role of antihistamines in the treatment of asthma is controversial and although they can offer partial protection against the early asthmatic reaction (EAR) [7] the effect on the late asthmatic reaction (LAR) is less certain [8]. The LAR to allergen inhalation challenge has features in keeping with on-going asthma and is associated with bronchial

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mucosal infiltration in which T cells and eosinophils are prominent [9].

Cetirizine protects against histamine challenge and may be helpful in seasonal allergic asthma [10,11]. Inhibition of eosinophil and basophil chemotaxis in allergen-induced late cutaneous responses has been suggested [12–15]. However, the effect of cetirizine in protecting against the development of allergen-induced LAR has yielded conflicting results [16,17].

The aim of this study was to determine the effect of cetirizine on EARs and LARs and the associated allergen-induced airways hyperresponsiveness. We have chosen a double-blind cross-over design to compare oral cetirizine with inhaled beclomethasone and a double dummy oral and inhaled placebo.

Methods

Patients

Twelve atopic patients with mild asthma (three male: nine female) were recruited from the Allergy Clinic, Royal Brompton Hospital, London, UK. Clinic details are documented in Table 1. A diagnosis of asthma was made from a history of episodic wheezing, chest tightness or cough, with evidence of $\geq 15\%$ variability in PEF_R, or FEV₁ within a 24 h period, either spontaneously or in response to β_2 -agonist treatment. All subjects exhibited airways hyperresponsiveness in response to methacholine inhalation challenge (PC₂₀ < 8 mg/mL). Atopy was confirmed either by an elevated total IgE level and the presence of specific IgE (Phadebas RAST) to house dust mite (*Dermatophagoides pteronyssinus*), timothy grass pollen (*Phleum pratense*) or cat dander, or by positive skin-prick tests to a range of common aero-allergens (house dust mite, timothy grass pollen, cat dander, tree pollen, dog hair, horse hair, feathers,

Aspergillus, *Cladosporium* and *Alternaria*). Individuals were non-smokers or had not smoked within the previous 6 months and not more than three cigarettes per day.

Subjects exhibited a LAR to inhalation challenge with an allergen to which they were sensitized. Inhalation challenges with grass pollen were performed out of season. Allergen challenge was not performed on any individual who gave a history of respiratory tract infection within the preceding 4 weeks. None of the subjects were taking oral corticosteroids or had received any within the previous 6 months. Any individuals taking inhaled corticosteroids had stopped at least 4 weeks prior to commencement of the study. Four subjects were currently taking intermittent short-acting inhaled β_2 -agonists and two of these individuals had taken low dose inhaled corticosteroids up to 4 weeks prior to entry into the study. One individual had been taking an oral antihistamine (terfenadine) for mild symptoms of rhinitis but had stopped 2 weeks before starting the study. Subjects gave their written informed consent and the study was approved by the ethics committee of the Royal Brompton Hospital. Twenty-six subjects were originally enrolled. Twelve patients fulfilled all the entry criteria and subsequently completed the study. The main reason for exclusion was the absence of a predetermined late fall (6–9 h after allergen inhalation) in FEV₁ of 15% from baseline.

Study design

The study was a double-blind randomized balanced cross-over design in 12 subjects with mild-moderate

Table 1. Patient details

Number	12
Gender	3M 9F
Age (years)	mean 29.2 range (19–47)
FEV ₁ % predicted	mean 93.7 range (74–113)
Methacholine PC ₂₀ (mg/mL)	mean 1.82 mg/mL range (0.39–8.00)
Atopy (SPT +ve)	6HDM 4Cat 2GP

Skin-prick test (SPT); house dust mite (HDM); grass pollen (GP).

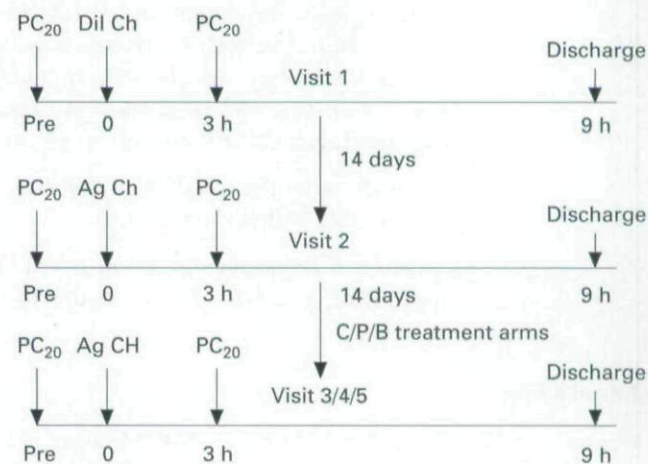


Fig. 1. Diagrammatic representation of study design. Dil Ch. Diluent challenge. Ag Ch. Allergen challenge. C,P,B represent cetirizine, placebo and beclomethasone, respectively, and PC₂₀ at 0 & 3 h represents methacholine inhalation challenge tests.

atopic asthma examining the effect of oral cetirizine, inhaled beclomethasone and placebo on the EAR and LAR to allergen inhalation challenge. To eliminate the influence of first order carry-over effect each treatment was preceded by each of the other two treatments the same number of times. Subjects attended for five visits separated by 14 days in order to allow for resolution of the increase in airways hyperresponsiveness seen after allergen challenge (Fig. 1).

At visit 1, skin-prick tests were performed, methacholine airways responsiveness recorded and FEV₁ documented hourly following a saline challenge. Visits 2–5 involved full day observation. Methacholine airways responsiveness was measured at 09.00 h and 15.00 h after allergen challenge prior to the development of the LAR. In all subjects FEV₁ had returned to within 90% of pre-challenge baseline values. Allergen inhalation challenges were commenced at 11.00 h allowing time for FEV₁ to return to baseline values following the 09.00 h methacholine inhalation test. Allergen challenge procedures performed during visit 2 documented the size of the LAR, confirming eligibility to continue with the study protocol. If a fall in FEV₁ $\geq 15\%$ was not achieved the subject was excluded from the study at this stage. Allergen challenges after treatment were performed during visits 3–5.

Treatment regimens were oral cetirizine 15 mg twice daily or oral placebo for 3 days and cetirizine 15 mg or placebo on the morning of the challenge (09.00 h). Inhaled beclomethasone (500 μ g) or inhaled placebo were taken 10 min prior to allergen challenge. The three treatment arms were oral cetirizine and inhaled placebo, oral placebo and inhaled beclomethasone and oral placebo and inhaled placebo in random order and double-blind. Compliance was assessed by counting the returned tablets and if not 100%, the subject was excluded. Oral and inhaled preparations taken on the day of the challenge were done so in the presence of the attending physician (A.M.B.).

Methacholine inhalation tests

Methacholine inhalation tests were performed by a tidal breathing method using a Wright nebulizer [18]. Solutions were used at room temperature and nebulizer output was calibrated to produce 0.13 mL/min for 2 min (total 0.26 mL). Nebulizer output was checked monthly using a rotameter. Initially subjects' resting FEV₁ (best of three forced expiratory manoeuvres) was recorded using a Vitalograph spirometer. A control solution of 4 mL of 0.9% saline was placed in the nebulizer container and was inhaled by the subject for 2 min via a loosely fitting mask with the nose clipped. FEV₁ (single forced

expiratory manoeuvre) was recorded at 30 s, 90 s and 3 min after each inhalation. At 5 min intervals doubling concentrations of methacholine from 0.03 mg/mL to a maximum of 32 mg/mL were inhaled with FEV₁ (single forced expiratory manoeuvre) recorded at 30 s, 90 s and 3 min. Inhalations were terminated when a fall in FEV₁ at 30 s or 90 s of $\geq 20\%$ from the lowest post-saline challenge value was recorded.

Results were plotted with percentage change in FEV₁ on a linear scale against methacholine concentration on a logarithmic scale. PC₂₀ (provocative concentration of methacholine resulting in a 20% fall in FEV₁) was obtained by linear interpolation of the last two points on the log dose–response curve.

Allergen inhalation challenge tests

Allergen extracts were partially purified, biologically standardized, freeze-dried preparations from the same batch (ALK, Horsholm, Denmark). House dust mite, timothy grass and cat dander extracts were used for inhalation challenge procedures. Allergen extracts were reconstituted prior to use in diluent provided and subsequent serial dilutions were made in normal saline. Half log dilutions were made from 100 000 BU to 10 BU. The initial concentration of allergen used for inhalation was determined by prior skin-prick testing and taken as one half log concentration lower than that shown to result in a 2 mm skin weal on skin-prick testing.

Allergen inhalation tests commenced at 11.00 h during visits 2, 3, 4 and 5. Subjects' FEV₁ were recorded as the best of three forced expiratory manoeuvres. FEV₁ had returned to within 90% of baseline values following the prior methacholine inhalation challenge. Initial inhalation of 0.9% saline (2 min tidal breathing via a Wright nebulizer and loosely fitting mask with nose clipped) was undertaken. Subjects then inhaled half-log increasing concentrations of allergen for 2 min at 10 min intervals. FEV₁ (best of three forced expiratory manoeuvres) was recorded at 0, 5 and 10 min after each inhalation. The end point for a positive response was a 20% fall in FEV₁ after allergen compared with minimum post-saline value (EAR). If at 10 min the FEV₁ had fallen to between 10 and 20% of the lowest post-saline value, FEV₁ was recorded at 5 min intervals until a 20% reduction was observed or until FEV₁ returned to within 10% of lowest post-saline value. The next concentration of allergen was then administered. When an immediate response was achieved the FEV₁ was recorded at 10 min intervals for 1 h and then hourly up to 9 h after the last dose of inhaled allergen. Challenges were performed in the presence of a physician (A.M.B.) with readily available resuscitation measures, including

Table 2. Methacholine PC₂₀ (geometric mean values) before and after allergen challenge and the effect of treatment with cetirizine and beclomethasone

	Methacholine PC ₂₀ before allergen challenge	Methacholine PC ₂₀ after allergen challenge	Ratio of methacholine PC ₂₀ before/after allergen	95% CI for geometric mean	P value
Cetirizine	1.30	0.59	1.80		
Beclomethasone	1.28	0.85	1.51		
Placebo	1.31	0.54	2.41*		
δ (Cet-Bec)	1.01	0.69	1.45	(1.02; 2.05)	<0.05
δ (Cet-Plac)	0.98	1.09	0.9	(0.63; 1.28)	NS
δ (Bec-Plac)	0.98	0.98	0.62	(0.44; 0.89)	<0.02

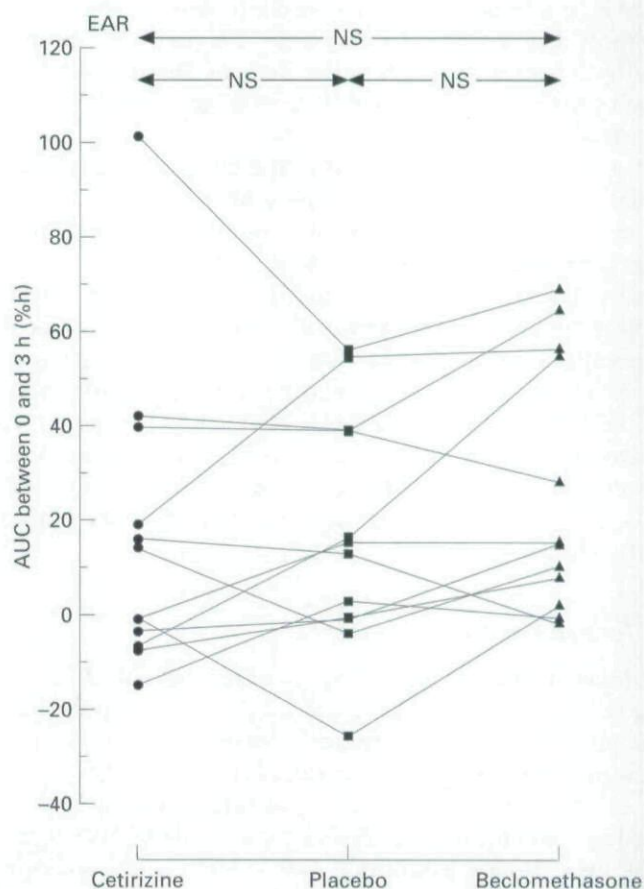
δ (Cet-Bec) difference between cetirizine and beclomethasone, δ (Cet-Plac) difference between cetirizine and placebo, δ (Bec-Plac) difference between beclomethasone and placebo.

0.5 mL of 1 in 1000 adrenaline drawn up in a syringe. After 9 h subjects were given two puffs of inhaled salbutamol (200 µg) and one puff of inhaled beclomethasone (250 µg) as a precaution prior to discharge home. A salbutamol inhaler was provided for home use and the telephone number of the attending physician supplied in the unlikely event of untoward bronchoconstriction. At visits 3, 4 and 5 only the last three concentrations of allergen administered at visit 2 were given as a single cumulative concentration.

EARs were recorded as the AUC (area under the curve between allergen and saline challenge) from 0 to 3 h and also as the maximum FEV₁% decrease between 0 and 3 h. The magnitude of the LAR was recorded as the AUC (between allergen and saline challenge) from 6 to 9 h and also as the maximum FEV₁% decrease 6–9 h after allergen administration. The 6–9 h time points were chosen in order to avoid the compounding effect the methacholine test at 3 h would otherwise have had on the size of the LAR. β₂-agonist medication was stopped 12 h prior to allergen challenge. Anti-histamine medication was stopped at least 48 h and up to 8 weeks prior to allergen challenge dependent on the duration of action of the drug taken. Subjects had not been taking inhaled steroids or theophylline preparations within 4 weeks of entering the study protocol.

Statistical analysis

Statistical analyses were performed using SPSS/PC+ and SAS computer software packages. Comparison of the effect of the three treatments on the early asthmatic response, late asthmatic response and methacholine PC₂₀ were in the first instance performed by an analysis

**Fig. 2.** Comparison of the effects of cetirizine, placebo and beclomethasone on the area under the curve (AUC) during the EAR (0–3 h) to allergen inhalation challenge.

of variance for a balanced three-way cross-over design carried out at the 5% significance level. This allowed the effect of treatment, be it cetirizine, placebo or beclomethasone, the effect of period of treatment (visit 3, 4 or 5) and an interaction between the two factors to be analysed. In the case of a globally significant difference between the three treatments, contrasts were used to compare the three treatments two by two using the ANOVA and significance tested at the 2% level.

Results

Twenty-six patients were screened and 12 fulfilled all criteria for eligibility, the remainder being excluded after the first visit in view of a lack of a documented late asthmatic response [19]. Methacholine and allergen inhalation challenges were well tolerated and there were no complications or episodes of untoward bronchoconstriction either during the procedures or afterwards. None of the subjects needed to contact the attending physician by telephone following discharge. Very few adverse effects of treatment were reported. There were two reports of somnolence and one of dry mouth whilst taking cetirizine. No patients received inhaled steroids or inhaled bronchodilators to reverse any untoward bronchoconstriction after challenge.

Baseline FEV₁ values were comparable for the three treatment arms and during the three study periods. The mean baseline FEV₁ % predicted values for visits 3, 4 and

5 were 92.9%, 92.7% and 93.8%, respectively. Similarly, there was no significant difference in basal FEV₁ % between selection visit 1, visit 2 and the three treatment periods (visits 3, 4, 5). Mean FEV₁ % predicted values at visits 1 and 2 were the same (93.7%). Baseline airways hyperresponsiveness was comparable at 9.00 h on each study day 2 h prior to allergen inhalation challenge (Table 2). No significant difference was observed among baseline geometric mean PC₂₀ measurements at visits 3, 4 and 5. The values were 1.34 mg/mL, 1.32 mg/mL and 1.22 mg/mL, respectively, and they did not differ significantly from the geometric mean methacholine PC₂₀ at the selection visit (1.82 mg/mL).

Early asthmatic response

The effect of cetirizine, beclomethasone and placebo on the size of the EAR is shown graphically in Fig. 2 and in Table 3. Neither cetirizine nor beclomethasone significantly inhibited the early asthmatic response when recorded as AUC (0–3 h) or as the maximum percentage fall in FEV₁ between 0 and 3 h. The mean size of the early response expressed as AUC (% decrease in FEV₁ hour⁻¹) after cetirizine was 16.5, after beclomethasone 26.3 and after placebo 17.0. Expressed as the maximum percentage fall in FEV₁ the mean size of the early response after cetirizine was 20.3, after beclomethasone 27.4 and after placebo 24.3. Although no specific treatment effect was observed, eight out of 12 subjects during

Table 3. Early asthmatic response (maximum percentage fall in FEV₁ 0–3 h)

Subject	Cet	Bec	Plac	δ (Cet-Bec)	δ (Cet-Plac)	δ (Bec-Plac)
1	3.4	13.3	10.2	-9.9	-6.7	3.2
2	38.8	44.0	46.2	-5.2	-7.4	-2.2
3	10.4	44.0	26.0	-33.6	-15.6	18.0
4	4.5	5.7	10.1	-1.2	-5.7	-4.4
5	40.3	46.7	30.6	-6.3	9.7	16.0
6	35.0	52.3	32.8	-17.3	2.2	19.5
7	7.4	9.7	11.3	-2.3	-3.9	-1.6
8	2.0	18.9	9.8	-16.8	-7.8	9.1
9	30.0	21.7	27.6	8.3	2.4	-5.8
10	5.5	5.7	19.6	0.4	-14.1	-14.5
11	52.2	47.8	43.5	4.3	8.7	4.3
12	13.8	20.0	24.5	-6.2	-10.6	-4.5
Mean	20.3	27.4	24.3	-7.2	-4.1	3.1
95% CI for mean				(-14.5; -0.8)	(-10.5; 2.3)	(-3.3; 9.5)

Cet (cetirizine), Bec (beclomethasone), Plac (placebo); δ (Cet-Bec) difference between cetirizine and beclomethasone, δ (Cet-Plac) difference between cetirizine and placebo, δ (Bec-Plac) difference between beclomethasone and placebo.

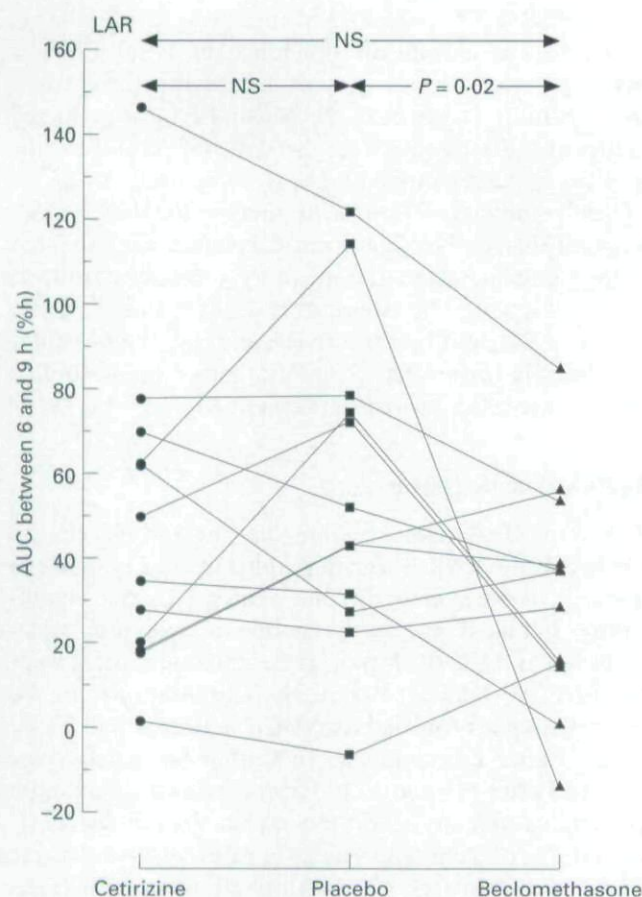


Fig. 3. Comparison of the effects of cetirizine, placebo and beclomethasone on the area under the curve (AUC) during the LAR (6–9 h) to allergen inhalation challenge.

the cetirizine arm exhibited a reduction in the size of the EAR compared with placebo and in five of these individuals there was a greater than 50% reduction of the size of the decrease in FEV₁. After beclomethasone six of 12 subjects exhibited a reduction in the size of the EAR although this was pharmacologically significant (>50% reduction in fall in FEV₁) in only one individual.

Late asthmatic response

The effects of cetirizine and beclomethasone on the LAR are shown in Fig. 3 and Table 4. Cetirizine did not inhibit the LAR compared with placebo. The mean size of the LAR expressed as AUC (6–9 h) after cetirizine was 48.9 and after placebo was 56.3. When expressed as percentage, maximum fall in FEV₁ from 6 to 9 h after cetirizine was 20.8 and after placebo was 24.6. Six subjects exhibited a reduction in size of the LAR, four of them showing a greater than 50% reduction in maximal late fall in FEV₁ between 6 and 9 h, with one subject exhibiting a

reduction in size of the LAR by just under half compared with placebo. Beclomethasone significantly inhibited the size of the LAR compared with placebo when expressed as AUC (6–9 h) ($P = 0.02$) (Fig. 3), and almost reached statistical significance ($P = 0.06$) when recorded as the percentage maximum fall in FEV₁ from 6 to 9 h (Table 4) (albeit at the 2% significance level for a two by two comparison). The mean size of the LAR after beclomethasone treatment expressed as AUC was 30.5 and as maximal fall in FEV₁ was 16.9.

Airways hyperresponsiveness to methacholine

Methacholine PC₂₀ was recorded prior to allergen challenge and at 3 h after challenge (when FEV₁ had returned to within 90% of baseline in all 12 subjects) and prior to the onset of a late asthmatic reaction. During the placebo arm there was a greater than twofold increase in airways hyperresponsiveness after allergen inhalation challenge (Table 2). An increase in airways responsiveness to methacholine (1.8-fold) was observed after allergen challenge following cetirizine treatment (Table 2). In contrast, beclomethasone inhibited the increase in airways hyperresponsiveness seen after allergen compared with both placebo ($P < 0.02$) and cetirizine ($P < 0.05$) (Table 2 and Fig. 4).

Discussion

We have used a double-blind placebo-controlled cross-over design to study the effect of 4 days pretreatment with cetirizine 15 mg bd, a single inhalation of 500 µg beclomethasone and placebo during the development of the EAR and LAR to allergen inhalation challenge in sensitized individuals. Cetirizine did not significantly inhibit the size of either the EAR or LAR. A single inhalation of 500 µg of beclomethasone did not inhibit the EAR but significantly inhibited the LAR and the associated increase in airways responsiveness 3 h after allergen inhalation challenge.

The two previous studies which examined the effect of cetirizine on EARs and LARs to allergen inhalation challenge have yielded conflicting results [16,17]. Wasserfallen *et al.* studied 16 atopic subjects in a double-blind parallel group design comparing 7 days pre-treatment with cetirizine 15 mg bd and placebo. Cetirizine was observed to significantly inhibit the LAR compared with placebo. There was no effect of cetirizine on the EAR. In the study by de Bruin-Weller 16 patients were recruited in a double-blind parallel group design comparing cetirizine 15 mg bd for 18 days with that of placebo. Cetirizine was not seen to inhibit the EAR or LAR and did not alter the airways responsiveness to methacholine.

Table 4. Late asthmatic response (maximum percentage fall in FEV₁ 6–9 h)

Subject	Cet	Bec	Plac	δ (Cet-Bec)	δ (Cet-Plac)	δ (Bec-Plac)
1	8.6	18.3	16.9	-9.7	-8.3	1.4
2	24.5	8.0	48.1	16.5	-23.6	-40.1
3	8.3	26.0	20.0	-17.7	-11.7	6.0
4	25.4	8.6	30.4	16.8	-5.1	-21.9
5	29.0	15.0	12.9	14.0	16.1	2.1
6	8.3	15.4	34.4	-7.1	-26.1	-19.0
7	51.5	33.9	45.2	17.6	6.3	-11.3
8	10.2	18.9	17.6	-8.7	-7.4	1.2
9	30.0	29.0	29.3	1.0	0.7	-0.3
10	25.5	5.1	19.6	20.4	5.9	-14.5
11	23.9	17.4	19.6	6.5	4.3	-2.2
12	4.3	7.4	1.1	-3.1	3.2	6.3
Mean	20.8	16.9	24.6	3.9	-3.8	-7.7*
95% CI for mean				(-4.3; 12.0)	(-12.0; 4.4)	(-15.8; 0.5)

* $P = 0.06$ (two by two comparisons interpreted at 2% level of significance).

Cet (cetirizine), Bec (beclomethasone), Plac (placebo); δ (Cet-Bec) difference between cetirizine and beclomethasone, δ (Cet-Plac) difference between cetirizine and placebo, δ (Bec-Plac) difference between beclomethasone and placebo.

We have used a different study design incorporating a three-way cross-over phase with placebo, cetirizine and beclomethasone. Inhaled steroids taken 10 min prior to allergen inhalation challenge have previously been shown to inhibit the late phase response and associated increase in airways responsiveness [20]. However, in that study the interpretation was confounded by lack of randomizing the placebo day along with the randomized treatment days. Our design reduced bias to a minimum which is otherwise encountered with a parallel group design. Order and carry-over effects are potential problems with a cross-over study design. In this study comparable basal FEV₁ and methacholine PC₂₀ at each visit indicated that spacing between the allergen challenge visits was adequate and there was no effect of the treatment order. The development and size of the late asthmatic reaction can be variable between and within individuals at different times [21]. Under identical challenge conditions and attention to the timing of challenge procedures any variability would tend to cancel out. For these reasons in this study any effects observed on the EAR, LAR and airways responsiveness are indeed treatment effects.

A characteristic feature of the late asthmatic response to inhaled allergen is an increase in airways responsiveness seen after challenge and persisting for several days [18]. An increase in airways hyperresponsiveness was observed as early as 3 h after allergen challenge prior to

the development of the LAR [22]. This finding was confirmed in our current study. Our current finding that inhaled steroids inhibited both the 3 h increase in airways responsiveness and LAR whereas cetirizine did not inhibit either, demonstrates that it was not possible to pharmacologically dissociate the early increase in airways hyperresponsiveness from the subsequent LAR. We have previously shown a good correlation between the size of early changes in airways hyperresponsiveness and subsequent LARs [22]. The current observations lend support to our view that the early increase in airways responsiveness (and presumed underlying inflammation of the airways) precede the LAR and may possibly be necessary for the development of the LAR. Furthermore it would suggest that treatments which inhibit the early increase in airways responsiveness inhibit the subsequent LAR whereas treatments which do not inhibit the early increase in airways responsiveness do not.

In keeping with previous reports [16,17] cetirizine was not observed to significantly inhibit the EAR. It is perhaps a little surprising when a number of other antihistamines have been shown to offer up to 50% protection against the development of the early response [7,8]. However, eight out of 12 subjects did have a reduction in the size of the early response compared with placebo and in five of these cases there was >50% inhibition. Beclomethasone on the other hand resulted in

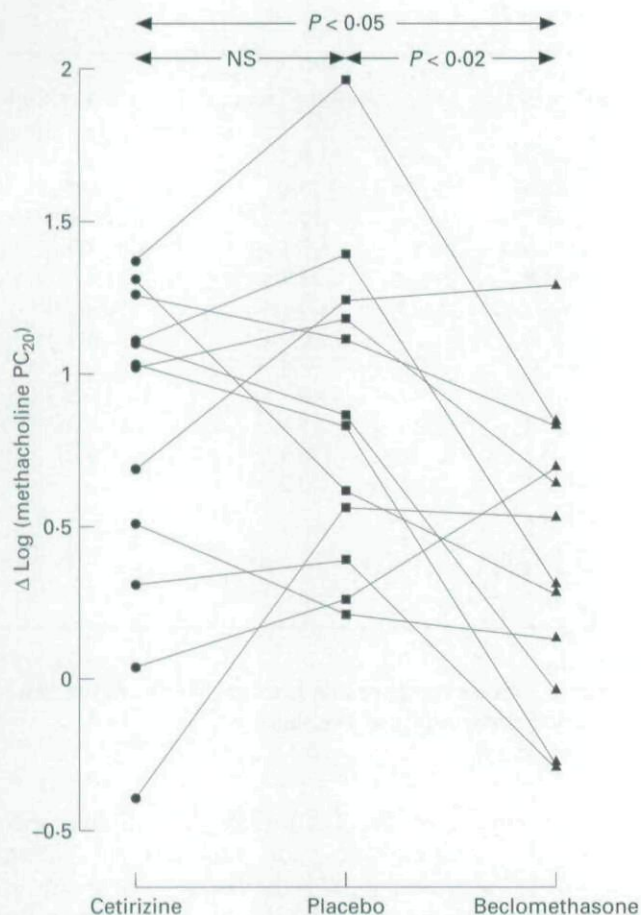


Fig. 4. Comparison of the effect of cetirizine, placebo and beclomethasone on the change in methacholine PC_{20} before and 3 h after allergen inhalation challenge.

a reduction in the size of the early response in six subjects with only one by >50%. It is possible that with more subjects studied cetirizine may result in a statistically significant inhibition of the EAR. A major criterion for eligibility was an EAR of at least 20% fall in FEV_1 . This was achieved in all subjects. However, four subjects during the placebo treatment arm exhibited an EAR of only 10% fall in FEV_1 thereby potentially making it more difficult for cetirizine to show a significant effect in comparison. However, these four subjects were within the eight out of 12 individuals in whom a reduction in the size of the EAR was observed during the cetirizine arm compared with placebo. They were not the four subjects in which cetirizine was not seen to exhibit an inhibitory effect on the EAR. Inhaled steroids are not known to reliably inhibit the EAR.

Cetirizine has been shown to have conflicting effects on the late response to allergen challenge. In the parallel

group study by Wasserfallen *et al.* [16] in which cetirizine afforded protection against allergen-induced LAR there was no accompanying measurement of airways responsiveness. By chance the LAR in the cetirizine group pre-treatment was greater than that of the placebo group thereby introducing bias. Furthermore, the FEV_1 at the 3 h time point was notably greater after cetirizine compared with pre-treatment perhaps suggesting a carry-over effect from the EAR. In the study by de Bruin-Weller [17] cetirizine was not observed to inhibit the LAR and there was no effect on the airways responsiveness to methacholine. The observation of no increase in airways hyperresponsiveness to methacholine following allergen challenge questions the allergen challenge methodology in view of many previous reports of increased responsiveness in association with LARs [18,22–24].

In our study beclomethasone partially inhibited the LAR to allergen inhalation challenge and offered protection against the associated increase in airways hyperresponsiveness after challenge. These observations confirm previous findings and the validity of experimental allergen challenge methodology. Eligibility for entry into the study was a maximal late fall in FEV_1 of 15% or greater. This was achieved in all cases. One subject on subsequent challenge after placebo treatment did not reproduce a late asthmatic response thereby reducing the number of late responders to 11. This is not surprising given the known inherent variability of the development of a LAR after repeated allergen challenge within the same individual [21]. Six subjects had a reduction in size of the LAR with cetirizine compared with placebo, four of which exhibited almost 50% reductions in FEV_1 . It is, however, unlikely that cetirizine is exerting a significant anti-inflammatory effect on the LAR. Effects on other regulatory mediators/cytokines remain to be determined.

In summary, in a double-blind placebo-controlled cross-over trial we did not show a significant effect of cetirizine on either the EAR or LAR to allergen inhalation challenge. Beclomethasone administered 10 min prior to allergen challenge inhibited both the LAR and the associated early increase in airways responsiveness. Furthermore, the increase in airways responsiveness was observed 3 h after allergen challenge prior to the development of a subsequent LAR. Although cetirizine is an effective, safe and highly selective H_1 antihistamine which has been shown to inhibit the migration of eosinophils and basophils in cutaneous late-phase reactions as detected by skin window techniques we have been unable to show any major effect on the size of the LAR. The use of cetirizine therefore cannot be advocated in the regular day to day management of asthma either for

symptomatic relief or anti-inflammatory prophylaxis. Its effectiveness, however, in seasonal and perennial allergic rhinitis and chronic urticaria is well established.

Finally, our study demonstrates the lack of pharmacological dissociation of early (3 h) changes in airways responsiveness and the subsequent LAR, compatible with our view that changes in PC₂₀ and underlying airways inflammation precede the LAR and may possibly be necessary for development of airway narrowing during the subsequent LAR.

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