

SHORT REPORT

Appearance of allergen-induced increases in airway responsiveness only after repeated allergen inhalations in two subjects

D. W. COCKCROFT*, R. E. RUFFIN† and F. E. HARGREAVE‡

*Section of Respiratory, Department of Medicine, University Hospital, Saskatoon, Saskatchewan, Canada,

†Department of Medicine, Flinders Medical Centre, Bedford Park, South Australia, Australia, and ‡Firestone Regional Chest and Allergy Unit, St Joseph's Hospital, 50 Charlton Avenue East, Hamilton, Ontario, Canada

Introduction

Allergen-induced late asthmatic responses (LAR) and increases in non-allergic airway responsiveness are important in the pathogenesis of both seasonal and perennial allergic asthma [1]. Boulet *et al.* have demonstrated that subjects who experience LARs and increases in airway responsiveness following bronchoprovocation with allergen in the laboratory also demonstrate seasonal increases in airway responsiveness and seasonal exacerbations of asthma [2]. In a study of the effects of ipratropium bromide on allergen-induced asthma [3], we noted that two of the four subjects who initially had an isolated early asthmatic response (EAR) with no induced increases in airway responsiveness developed definite increases in airway responsiveness and equivocal LARs following the second or third allergen tests. These data are presented and discussed with regard to the pathogenesis of asthma and with regard to the appropriate design of clinical investigations utilizing repeated allergen inhalation tests.

Subjects and methods

The two subjects were healthy young non-smoking females aged 24 and 18, with seasonal allergic rhinitis and asthma exclusively during the ragweed pollen season, with normal lung function and borderline (8–16 mg/ml) to normal (> 16 mg/ml) histamine PC₂₀ [4] when tested out of season, and skin-test endpoint sensitivity (smallest allergen concentration producing a 2-mm weal) of > 1:1024 of ragweed extract (stock solution 40 000 PNU/ml, Greer Laboratories Inc., Lenoir, NC 28645, U.S.A.).

Correspondence: Dr D. W. Cockcroft, Section of Respiratory, Department of Medicine, University Hospital, Saskatoon, Saskatchewan, Canada S7N 0X0.

Subjects were studied on 4 days outside the ragweed pollen season when the FEV₁ had <5% variability, the histamine PC₂₀ was stable, there was no medication use, allergen exposure or respiratory infection for >4 weeks.

Controlled allergen inhalation tests [3] were performed as follows. Day 1 was a control day, on which Coca's alkaline solution was nebulized (Wright nebulizer) and inhaled for 0.5, 1.0 and 0.5 min tidal breathing at 10-min intervals. The FEV₁ was measured initially in triplicate then in duplicate 10 min after each inhalation, and following the last inhalation every 10 min for the first hour, every 30 min for the second hour, and hourly for the next 6 hr. The highest reading at each time was retained. On Day 2, doubling amounts of allergen were inhaled at 10-min intervals commencing three doses below the predicted allergen PC₂₀, and continued until a 15–20% FEV₁ fall was achieved; FEV₁ was then followed as on Day 1. The EAR was defined as the largest percentage fall in FEV₁ in the first hour, and the LAR as the largest FEV₁ fall between 3 hr and 8 hr.

On Days 3 and 4, at intervals of ≥6 days, ipratropium bromide (80 µg) and placebo inhaler (four puffs), respectively, were administered single-blind 45 min prior to the completion of the allergen inhalation test with the same dose of allergen used on Day 2. FEV₁ expressed as percentage change from pre-treatment value, was recorded as on Days 1 and 2. In Subject 1, histamine PC₂₀ [4] was determined 2 days before (8 hr after saline control) and 8 and 32 hr after the initial allergen challenge, the day before and 8, 32 and 56 hr after the second allergen challenge, and the day before and 8 hr and 8 days after the third allergen challenge. In Subject 2, histamine PC₂₀ was measured the day before (8 hr after saline control) and

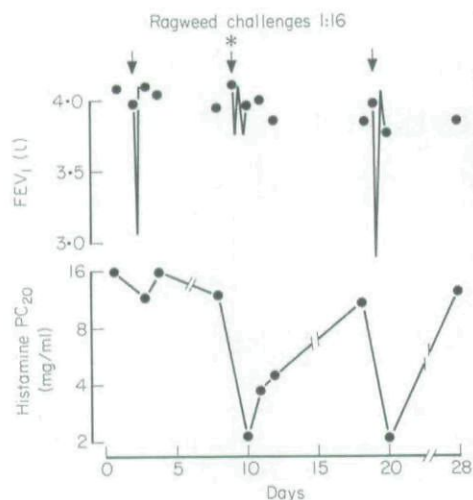


Fig. 1. Subject 1: FEV₁ (l) and histamine PC₂₀ (mg/ml) on the vertical axis and time (days) on the horizontal. Three identical ragweed inhalation challenges (1:16 × 30 sec) were done as noted by the arrows, the second (*) preceded by 80 µg ipratropium bromide.

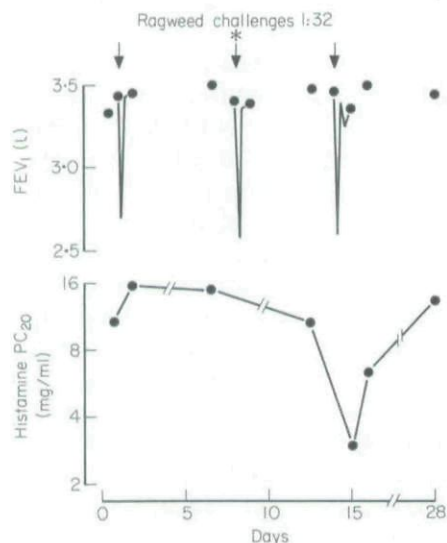


Fig. 2. Subject 2: FEV₁ (l) and histamine PC₂₀ (mg/ml) on the vertical axis and time (days) on the horizontal. Three identical ragweed inhalation challenges (1:32 × 30 sec) were done as noted by the arrows, the second (*) preceded by 80 µg ipratropium bromide.

8 hr after the first allergen challenge, the day before the second allergen challenge, and the day before and 8 hr, 32 hr and 13 days after the third allergen challenge.

Results

FEV₁ and histamine PC₂₀ values are plotted over the 4-week period in both subjects in Figs 1 and 2. Subject 1

(Fig. 1) initially developed a 30% EAR with no (0% FEV₁ fall) LAR or change in histamine PC₂₀. Following the second challenge, the EAR was reduced to 8% by ipratropium bromide. There was an 8% LAR and a 5.8-fold reduction in histamine PC₂₀ at 8 hr and a 3.2- and 2.6-fold reduction at 32 and 56 hr, respectively. The third allergen challenge (after placebo) gave a 30% EAR, a 5% LAR and a 5-fold reduction in histamine PC₂₀ which had recovered at 8 days.

Subject 2 (Fig. 2) had isolated 33% and 24% EARs on Days 2 and 3, respectively (LAR ≤ 1%), and had a 26% EAR with a 6% LAR on Day 4. There was no change in histamine PC₂₀ after the first allergen challenge; this was not assessed after the second allergen challenge. After the third allergen challenge there was a 3.5-fold reduction in histamine PC₂₀ at 8 hr, which had recovered partially at 32 hr and completely at 13 days.

Discussion

These two subjects with similar clinical characteristics demonstrated isolated EAR with no increase in airway responsiveness following initial allergen challenge. Significant increases in airway responsiveness with equivocal LAR developed following the second and third allergen challenge in Subject 1 and following the third allergen challenge in Subject 2.

These data suggest that, at least occasionally, allergen exposure may lead to 'priming' with enhancement of the late inflammatory sequelae on subsequent exposure. Allergen priming has been identified in the nose [6] and has been suspected to occur in the lung [7]. Previous investigations have focused principally on the EAR [7], which is likely of limited importance in the pathogenesis of seasonal or perennial allergic asthma [1]. Repeated allergen challenges have at least the potential to produce acutely (independent of any changes in allergen-specific IgE) opposing effects. Allergen-induced increase in non-allergic airway responsiveness will result in enhanced responses to any bronchoconstrictor stimuli including the early response to inhaled allergen [5]. By contrast, the immunological mechanisms that lead to hyposensitization could result in reduced responsiveness. Thus, it is not surprising that Rosenthal *et al.* were unable to find any consistent trend towards either priming or tolerance, and also why they report poor reproducibility, ± 1 log (10-fold), of the EAR [7]. When factors known to affect airway responsiveness are controlled, when measured airway responsiveness is kept constant, and when repeat challenges are done with at least 5 days' interval, the EAR is reproducible to within ± 2 -fold [3,8]. Nevertheless, in these two subjects, despite the controls noted above, an apparent priming effect on the late inflammatory sequelae was seen, with no change in EAR.

While the EAR is likely mainly bronchospastic, the mechanism of the late sequelae is not completely understood. Data from animal studies as well as bronchoalveolar lavage data from human studies suggest that airway inflammation with eosinophils and possibly neutrophils is important for the production both of LAR and of increases in airway responsiveness [9,10]. The mediator(s) responsible for the recruitment of the inflammatory cells, the source of the mediator(s) and the exact nature and source of the second wave of mediator(s) responsible for the increased airway responsiveness are not certain; this makes it difficult to speculate on how this system may be 'primed'. Possibilities would include failure of complete resolution of the inflammation despite return of airway calibre and airway responsiveness to baseline; increased 'recruitability' of the inflammatory cells; and increased 'mediator releasability' of inflammatory cells. The exact prevalence and precise mechanism of this phenomenon may have a great deal of importance in the pathogenesis of naturally occurring seasonal allergic asthma.

This may also be relevant in the design of clinical investigations into the pharmacological inhibition of the LAR. We regularly perform two unmedicated allergen challenges in such studies on the first and last days [3,8] to guard against any consistent change in responses. In 22 individuals [3,8] there was no consistent difference in the magnitude of the first and last LAR; the second LAR was larger in 11, smaller in eight and unchanged in three. Nevertheless, the occurrence of a progressive enhancement in allergen-induced increase in airway responsiveness in even a few subjects stresses the importance of assessing reproducibility of the late sequelae.

Summary

Observations in two subjects undergoing three allergen challenges for a drug study suggested 'priming' of the late sequelae, namely allergen-induced increase in airway responsiveness. Both subjects had rhinitis and asthma limited to the ragweed season, near normal out-of-season histamine PC₂₀, and extreme IgE sensitivity to ragweed. Both had an isolated early response with no change in histamine PC₂₀ after the first allergen challenge. Significant (3.5- to 5.8-fold) reductions in histamine PC₂₀ occurred after the second and third allergen challenge in Subject 1, and after the third challenge in Subject 2; this

was associated with equivocal 5-8% late responses. Such a 'priming' effect, the prevalence of which is not known, may be important in the pathogenesis of naturally occurring allergic asthma, and in the design of clinical trials involving repeated allergen inhalations.

Acknowledgments

The authors wish to thank Brenda Gore and Jacquie Bramley for their assistance in preparing the manuscript.

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