

Chapter 11

Bronchial Allergen Challenges: Doubling or Quadrupling Dose Steps?

S. Mousalli, V. van Kampen, and R. Merget

Abstract Inhalation challenges with allergens are considered the gold standard for the diagnosis of occupational asthma. However, no standardized methods are available. One open question is the degree of dose augmentation in the stepwise challenge protocols. Recently, it was recommended to increase the allergen concentrations by no more than doubling between dosing steps for safety reasons. We analyzed retrospectively our dosimeter allergen challenges performed with quadrupling dose steps during the last 10 years. Allergens were inhaled by an APSpro dosimeter and a DeVilbiss 646 nebulizer. The test was terminated after a fall of FEV₁ of at least 20%. Seventeen tests in 13 subjects were considered positive. The mean FEV₁ decreases 10 and 20–30 min after the last allergen dose were 26.7 ± 6.4 and $26.2 \pm 6.5\%$ baseline, respectively. Terminal dose response slopes did not differ between doubling (Cockcroft and Davis, *J Allergy Clin Immunol*, 122:1034–1035, 2008) and quadrupling doses, nor were there any differences concerning the maximal responses. The results suggest that quadrupling dose steps may be an acceptable alternative, without serious increase in risk of severe asthmatic reactions. We assume that by shortening the test duration, physicians might choose lower starting doses and thus make allergen inhalation challenges safer.

Keywords Allergen challenge • Asthma • Inhalation • Dose-response slope • Dosimeter • Tidal volume breathing

11.1 Introduction

Inhalation challenges with allergens are considered the gold standard for the diagnosis of occupational asthma. However, no standardized methods are available. One open question is the degree of dose augmentation in the stepwise challenge protocols. Recently, Cockcroft and Davis (2008) have recommended increasing the allergen concentrations by no more than doubling between dosing steps for safety reasons. These authors compared retrospectively the dose-response slopes of the last two doses of methacholine and allergen in the same individuals. The mean forced expired volume in 1 s (FEV₁) decrease at the second-to-last concentration of allergen was significantly lower than that seen for the second-to-last concentration of methacholine. However, the ratio of the last to

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second-to-last response (slope) was higher for allergen than for methacholine. A direct comparison of doubling and quadrupling allergen doses has not been performed.

We reviewed allergen challenges with quadrupling doses performed in our laboratory over the past 10 years that we considered positive. Inspired by Cockcroft and Davis (2008), we analyzed retrospectively our dosimeter allergen challenges.

11.2 Methods

In contrast to Cockcroft and Davis (2008) who used a tidal volume breathing method, the allergen was inhaled with 5 or 10 breaths (depending on the allergen) by an APSpro dosimeter (Jaeger, Würzburg, Germany) and a DeVilbiss 646 nebulizer (DeVilbiss Healthcare, Mannheim, Germany). Inhalations were performed as described by the ATS for methacholine challenges, with minor modifications (American Thoracic Society 2000; Merget et al. 2009). Ten-minute intervals were chosen between dose steps. The test was terminated if a fall of FEV_1 of at least 20% occurred within 30 min after allergen inhalation. After termination, another measurement was performed about 20–30 min after stopping the allergen inhalation. If a fall of FEV_1 between 15% and 19% was measured (near positive), spirometry was performed after another 10 min. Isolated late reactions were not included.

All spirometric maneuvers were performed according to the ATS and met reproducibility criteria (American Thoracic Society 1995). All subjects were without medication that might influence the test results. Inhalations were performed for the diagnosis of occupational asthma and approved by the Ethics Committee of the Ruhr University. Allergens were platinum salts ($n=7$ tests; final dose range 175–700 ng), rhodium salt ($n=1$; 36 ng), barn mites ($n=3$; 1,125–18,000 ng protein), house dust mites ($n=3$; 4,500–18,000 ng protein), α -amylase ($n=1$; 616 ng protein), cow dander, and soapnut ($n=1$ each; 348 and 2,814 ng protein).

11.3 Results

Seventeen tests in 13 subjects were considered positive. The mean age was 41 ± 14 years. The mean baseline FEV_1 was 95.5 (83.1–132.2)%predicted (Quanjer et al. 1993). The mean FEV_1 decreases 10 and 20–30 min after the last allergen dose were 26.7 ± 6.4 and $26.2 \pm 6.5\%$ baseline, respectively. The maximal decreases of FEV_1 after 10 and 20–30 min were not different either, amounting to 39% baseline after 10 min and 37%baseline, respectively. All positive reactions occurred after the second dose step or later. One subject preferred to inhale a short acting bronchodilator after the reaction had been documented. Terminal dose-response slopes did not differ between doubling (values from Cockcroft and Davis 2008) and quadrupling doses, nor were there any differences concerning the maximal response (Fig. 11.1). There was no difference between high and low molecular weight substances (data not shown). All but two positive reactions occurred after 10 min (two near positive reactions).

11.4 Discussion

The results of this retrospective analysis of routine challenge tests need to be interpreted with caution due to a low number of subjects. However, such data are difficult to obtain because they can be performed only with few occupational allergens that are water-soluble and there are often subjects' characteristics such as severe asthma, need for medication or unrelated diseases that represent

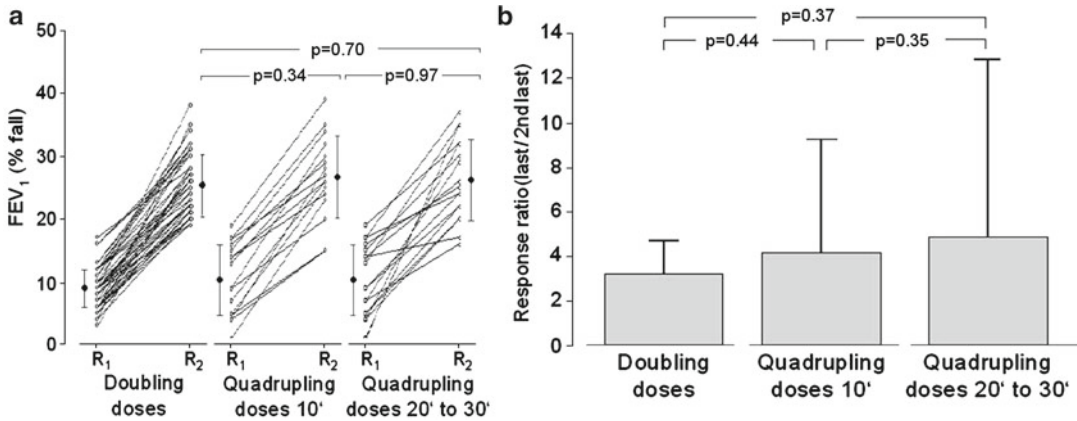


Fig. 11.1 (a) Individual terminal dose-response-slopes (means $\pm$ SD). A decline of FEV₁ from baseline after the second-to-last dose is designated R₁, after the last dose – R₂. FEV₁ values after doubling doses were provided by Cockcroft and Davis (2008) (n=54). FEV₁ values after quadrupling doses (n=17) are shown as 10 and 20–30 min after allergen inhalation; (b) Mean ratios of FEV₁ decline defined as R₂ divided by R₁. Comparisons were performed by paired and unpaired two-sided *t*-test

contraindications for the challenges. Prospective controlled studies are unlikely to be performed and a comparison between different methods may be questioned due to ethical reasons.

We are aware of the fact that a comparison of the present data with the literature data cannot be performed, because the methods differed in many respects. However, as no direct comparisons are available in the literature, we wanted to provide a rough estimate about the effects of increasing the dosing steps by more than doubling. Also, the different inhalation methods (tidal volume breathing method with doubling concentrations vs. dosimeter method with quadrupling doses) should not bias the comparison to a relevant degree, as dosing intervals, but not absolute doses, were compared.

A further weakness of this study is the lack of standardization with respect to the number of breaths during each inhalation step. This is due to the retrospective design of the study. By increasing breath numbers we applied a higher allergen dose, which was considered important for allergens that were less potent. However, we believe that this should not bias our results to a high degree.

Considering safety aspects, the maximal fall of FEV₁ after quadrupling doses was acceptable and was not different from Cockcroft and Davis' (2008) maximal decreases. Also complications such as severe asthma exacerbations needing medication did not occur. However, somewhat steeper dose-response slopes and higher standard deviations of the final dose-response slopes indicate that further increases of dosing intervals should not be considered.

Although the selection bias cannot be excluded, the study suggests that quadrupling doses may be performed without notable increase in risk of severe asthmatic reactions. This is accompanied by a noticeable shortening of the test duration. It should be noted that in the present study near-positive reactions did not immediately entail the next inhalation step, but a further spirometry was performed after another 10 min for safety reasons. We assume that by shortening the test duration, physicians might choose lower starting doses and thus make allergen inhalation challenges even safer. However, further observations about the potential risk of dose augmentation in allergen challenges are needed, preferably in prospective studies in larger numbers of subjects.

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Conflicts of Interest: The authors declare no conflicts of interest in relation to this article.

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