

Pattern of specific airway response in asthma due to western red cedar (*Thuja plicata*): relationship with length of exposure and lung function measurements

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Summary

In order to investigate the relationship between the pattern of response (immediate, late and dual) to specific bronchial challenge test with plicatic acid or red cedar extract and the clinical features of asthma, 332 patients with asthma induced by western red cedar dust were examined at the time of diagnosis. Specific challenge test induced in thirty-one patients (9.3%) an isolated immediate reaction, in 144 patients (43.4%) an isolated late reaction and in 157 patients (47.3%) a dual reaction. Patients with a dual reaction had a longer period of exposure to red cedar dust between the onset of the respiratory symptoms and the time of the definitive diagnosis, a lower FEF_{25-75%} and a greater degree of non-specific bronchial hyperresponsiveness compared to patients with isolated immediate or isolated late reactions; the difference in bronchial hyperresponsiveness to methacholine among the three groups persisted when the values were adjusted for the different baseline value of FEV₁. There was no difference in the prevalence of specific serum IgE antibodies to plicatic acid-human serum albumin conjugate among the three groups of patients with different type of response to red cedar. Except for the greater degree of non-specific bronchial hyperresponsiveness, patients with isolated late reactions were not different from those with isolated immediate reactions in other clinical findings. These findings indicate that a dual reaction in patients with occupational asthma due to simple chemical agents is indicative of a greater severity of disease at diagnosis. The pathogenetic mechanism of various types of asthmatic reaction is unknown and it is likely to be different between isolated immediate and isolated late reactions.

Introduction

Bronchial asthma due to western red cedar (*Thuja plicata*) is one of the most important types of occupational asthma with regards to the number of affected workers [1]. Plicatic acid, a low molecular weight compound isolated from western red cedar, was

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found to be the agent responsible for the asthmatic reaction [2]. Inhalation challenge test with plicatic acid or red cedar extract can result in an immediate bronchospastic reaction, an isolated late reaction or a dual (both immediate and late) reaction; late and dual reactions account for about 90% of all positive responses to specific challenge tests [3], as observed in other types of occupational asthma caused by low molecular weight compounds [4,5]. The pathogenetic mechanisms and the clinical significance of the different patterns of response to specific bronchial challenge tests are not well understood. In allergic bronchial asthma due to common allergens, some investigators observed that a dual reaction was associated with a more severe disease compared to those who developed an isolated immediate reaction [6,7]. In occupational asthma, there are few studies concerning this issue [3,5,8]. In a previous study on 206 patients with red cedar asthma, Lam *et al.* [3] observed that subjects with a dual response to plicatic acid challenge had a longer duration of symptoms before diagnosis compared to subjects with isolated immediate or isolated late responses; they also had lower pulmonary function and a greater degree of non-specific bronchial hyperresponsiveness.

This is an extension of the previous study [3] on 332 patients with red cedar asthma to investigate the clinical significance of the different patterns of bronchial response, by searching for any relationship between the type of specific bronchial response to inhalation challenge with red cedar extract and the clinical features of the disease, such as duration of symptoms, allergic sensitization, airway obstruction and non-specific bronchial hyperresponsiveness.

Patients and methods

Patients

Three hundred and thirty-two patients with red cedar asthma (including 206 previously reported) were seen at the University of British Columbia Respiratory Clinic. The aetiological diagnosis was confirmed in all patients by specific inhalation challenge test either with the crude extract or with plicatic acid. Specific or non-specific challenges were carried out after the patients had been away from exposure for at least 1 week.

Pulmonary function tests

Forced expiratory volume in 1 sec (FEV_1), forced vital capacity (FVC) and maximal mid-expiratory flow rate (FEF 25–75%) were measured using a 13.5 litre Collins water spirometer. Predicted values were derived from Morris *et al.* [9] for the whites and from Corey *et al.* [10] for the non-whites.

Methacholine inhalation challenge

The details of the test have been previously reported [11]. Aerosols of phosphate buffered saline followed by doubling concentrations of methacholine (0.03 to 24 mg/ml) were inhaled for 2 min and FEV_1 was measured 30 sec and 4 min after each inhalation. A positive result was indicated by a decrease in FEV_1 of more than 20% from post-saline value. The provocative concentration of methacholine that induced a 20% decrease in FEV_1 (PC₂₀) was determined from the dose-response curve. Methacholine inhalation test was conducted when the patients have been away from occupational exposure for at least 1 week and without bronchodilator therapy for at least 12 hr.

Table 1. Clinical findings of patients with immediate, late or dual reactions to specific inhalation challenge test

	Immediate	Late	Dual
Number	31	144	157
Age (years)	37.3 $\pm$ 9.8	39.4 $\pm$ 12.6	40.1 $\pm$ 11.9
Race: non-whites	16 (52%)	56 (39%)	79 (50%)
Smoking habit: non-smokers	22 (71%)	91 (63%)	112 (72%)
Duration of exposure			
before symptoms (months)	51.9 $\pm$ 51.4	36.5 $\pm$ 51.6	42.6 $\pm$ 64.2
Duration of symptoms			
before diagnosis (months)	16.2 $\pm$ 18.2	21.3 $\pm$ 32.8	30.7 $\pm$ 41.9*
Allergy skin tests positive	15 (48%)	44 (30%)	61 (40%)
Specific IgE levels			
RAST ratio > 2	4 (26%)	13 (21%)	15 (26%)

* Significant difference between groups (variance analysis; $P < 0.01$).

Inhalation challenge test

It was performed as previously described [3] and always 24 hr after pulmonary function tests and methacholine inhalation challenge. Briefly: after a control test with phosphate buffered saline, the next day the patient inhaled red cedar extract or plicatic acid (5 mg/ml in phosphate buffered saline pH 7.4) at tidal breathing from a Bennet twin nebulizer (flow rate: 5 litres/min; output: 0.25 ml/min); the solution was inhaled for 0.5, 1, 1.5 and 2 min at 10-min intervals and FEV₁ was measured 10 min after each inhalation. The test was terminated when a fall in FEV₁ greater than 20% from baseline value occurred or after a total of 5-min inhalation. FEV₁ was measured at 10, 20, 30 and 60 min and thereafter at hourly intervals until 8 hr after challenge and again at 24 hr. A reaction was defined as a response in which there was a decrease in FEV₁ greater than 20% from the baseline value. The response was considered as immediate, when a fall in FEV₁ occurred within the first hr from the challenge; as late, when FEV₁ dropped between the second and the eighth hour; and as dual, when the immediate reaction with spontaneous recovery within 1–2 hr was followed by a late reaction.

Allergy skin tests

Prick tests were done with the following extracts of common allergens (Bencard Allergy Service): house dust mite, *Dermatophagoides culinae*; feathers, *Alternaria*, *Cladosporium herbarium*, *Aspergillus fumigatus*, *Sporobolomyces*, *Candida albicans*; dry rot; mixed Pacific grass, tree and weed pollens; cat and dog hair; horse danders; milk, egg, wheat, fish and nuts. A weal greater or equal to 3 mm was considered as a positive response. Extract of red cedar (10% w/v) and plicatic acid (5 mg/ml) were also used for skin testing by the prick method.

Specific IgE antibodies to plicatic acid

Plicatic acid was conjugated to human serum albumin (HSA) and the patient's sera were tested for the presence of specific IgE antibodies to plicatic acid–HSA conjugate using the radio-allergo-sorbent test (RAST) as previously described [12]. The RAST

Table 2. Spirometric values (mean $\pm$ s.d.) of patients with immediate, late or dual reactions to specific inhalation challenge test

	Immediate	Late	Dual
FEV ₁ (l)	3.43 $\pm$ 0.79	3.37 $\pm$ 0.79	3.13 $\pm$ 0.75
(% predicted)	99.0 $\pm$ 17.0	97.3 $\pm$ 17.9	93.6 $\pm$ 19.7
FVC (l)	4.76 $\pm$ 1.13	4.61 $\pm$ 0.95	4.52 $\pm$ 0.91
(% predicted)	106.5 $\pm$ 14.0	102.6 $\pm$ 14.4	104.2 $\pm$ 16.4
FEF 25–75 (l/sec)	2.96 $\pm$ 1.32	2.75 $\pm$ 1.19	2.36 $\pm$ 1.08
(% predicted)	77.7 $\pm$ 32.3	73.0 $\pm$ 29.3	64.3 $\pm$ 27.3*

* Significant difference between groups (variance analysis; $P < 0.01$).

ratios of serum specimens were expressed as multiples of the base-line radioactivity from the pooled serum samples from normal subjects; a ratio greater than 2.0 was considered as indicative of the presence of specific IgE antibodies.

Statistical analysis

Analysis of variance and chi-square test were performed for statistical evaluation. Logarithmic transformation of PC₂₀ was used for statistical analysis; PC₂₀ values of different groups were adjusted for baseline FEV₁ and other clinical findings by covariance analysis.

Results

The clinical findings of the 332 patients are reported in Table 1. There was no difference between the first group of 206 patients of the previous study and the further 126 patients as regard to all clinical and functional data, except for the immediate skin reaction to one or more common allergens, which was significantly greater in the second group of patients (50% *vs* 28%, respectively). Thirty-one patients only (9.3%) had an immediate reaction to plicatic acid while most of the patients had a late (43.3%) or a dual (47.3%) reaction. There were no significant differences between the three groups of patients with immediate, late or dual reactions as regards age, race, sex and smoking habit; most of the patients were non-smokers. The patients who, at diagnosis, showed a dual reaction had a more prolonged period of exposure between the onset of respiratory symptoms and when the definitive diagnosis was made. Positive immediate skin reaction to one or more common allergens was observed in 48% of patients with an immediate reaction and in 30 and 40% of patients with late or dual reactions, respectively; however, the differences between the three groups were not significant. Specific IgE determination was performed on 138 patients; an elevated level of specific IgE to plicatic acid–HSA conjugate was observed in thirty-two patients (22.2%). There was no difference in the per cent of patients with specific IgE antibodies among the three groups of patients.

The results of pulmonary function tests at the time of diagnosis are shown in Table 2. Subjects with dual response had lower FEV₁ and FEF 25–75% compared to patients with the other patterns of response; the differences between the groups reached the level of statistical significance for FEF 25–75%.

Table 3. Bronchial hyperresponsiveness (PC₂₀, geometric mean $\pm$ s.e., adjusted for baseline FEV₁) and spirometric values (mean $\pm$ s.d.) in patients with immediate, late or dual reactions

	Immediate	Late	Dual
Number	20	84	92
PC ₂₀ (mg/ml)	1.96 $\pm$ 1.47	1.25 $\pm$ 1.20*	0.64 $\pm$ 1.19†
FVC (% predicted)	109.6 $\pm$ 14.3	102.7 $\pm$ 13.4	106.2 $\pm$ 14.7
FEV ₁ (% predicted)	104.2 $\pm$ 15.5	98.3 $\pm$ 16.7	95.8 $\pm$ 16.9
FEF 25-75 (% predicted)	94.9 $\pm$ 31.8	72.7 $\pm$ 27.5	64.8 $\pm$ 28.1†

* Significant difference with the group with immediate reactions (unpaired Student's *t*-test; $P < 0.01$).

† Significant difference between groups (variance analysis; $P < 0.01$).

One hundred and ninety-six subjects had a methacholine challenge test at the time of diagnosis; there was no difference in clinical findings between the patients who had a methacholine inhalation test and those who did not have the test done. The results of pulmonary function tests and methacholine challenge in these patients are reported in Table 3. Subjects with a dual response on specific challenge showed a significantly lower mean PC₂₀ compared to subjects with isolated late or isolated immediate responses. Subjects with an isolated late reaction had significantly lower PC₂₀ compared to subjects with an isolated immediate reaction. Because differences in baseline airway calibre among the three groups of patients could explain the observed difference in the response of methacholine, PC₂₀ was corrected by multiple regression analysis for baseline FEV₁; there was a significant difference among the groups by analysis of covariance ($P < 0.01$), patients with a dual response showing the lowest value.

Discussion

Late asthmatic reaction is a very frequent finding in specific airway response to inhaled low molecular weight compounds causing occupational asthma. In our study only thirty-one (9.3%) out of 332 patients had an isolated immediate reaction to plicatic acid or red cedar extract, while isolated late and dual reactions were very common, 43.4% and 47.3%, respectively. This is in accord with previous reports of occupational asthma caused by other low molecular weight agents, such as diisocyanates [4,5] or colophony [13]. By contrast, in asthma caused by high molecular weight compounds such as pollens or house dust, an isolated late reaction is very unusual and the patients usually developed an isolated immediate or a dual reaction to a specific challenge test [6,7,14]. This different prevalence of isolated late asthmatic reactions is the main difference between asthma caused by high and low molecular weight compounds and it might be related to a different pattern of chemical mediators (released or newly synthesized) from different cell population of the airways. In effect, mast cell degranulation with release of histamine, chemotactic factors and prostaglandins is shown to be present in immediate and dual reactions to allergens [15], whereas recruitment of eosinophils and neutrophils in airway is observed during isolated late asthmatic reactions to western red cedar [16] or toluene diisocyanate [17].

In this study we confirmed, on a greater number of patients, what was previously described by Lam *et al.* [3]. Subjects with a dual reaction had a longer duration of

symptoms before diagnosis, a poorer initial pulmonary function and a more severe degree of non-specific bronchial hyperresponsiveness to methacholine, compared to subjects with isolated late or isolated immediate responses to plicatic acid. No difference was observed among the three groups as regards age, smoking habit, serum specific IgE levels and duration of exposure before the beginning of the symptoms. These data are in accord with previous reports about occupational asthma caused by other chemical agents [5,8] and confirm the observation that a dual reaction to specific challenge is indicative of a more advanced stage of the disease at the time of diagnosis. The majority of patients with red cedar asthma complained at the onset of their illness of asthmatic symptoms usually after working hours and at night. With continued exposure, they complained of symptoms during working hours; later on, symptoms occurred almost immediately on exposure. Thus, in natural history of occupational asthma due to low molecular weight compounds, a late reaction might change into a dual reaction with the persistence of the disease. Some authors observed that an increase in the administered dose of allergen or chemical agent during a specific challenge test or repeating the challenge using the same dose after a few days may change the pattern of airway response from late to dual reactions to a specific agent [3,18]. Furthermore, patients with a dual airway reaction to toluene diisocyanate showed a loss of the immediate airway response but a persistence of the late response some months after cessation of work (Mapp, unpublished data). A different degree of non-specific bronchial hyperresponsiveness and a different sensitivity to chemical mediators and/or a different pattern of chemical mediators released into airways might explain the difference among the three types of specific airway response to the same agent [19]. In effect, patients with a dual reaction had a higher non-specific bronchial hyperresponsiveness to methacholine in comparison with patients with isolated late and isolated immediate airway reactions; this fact was not ascribed to a greater airway obstruction in patients with a dual reaction, as the difference in methacholine PC₂₀ among the three groups persisted even after adjustment for the different level of baseline FEV₁.

Allergic sensitization to common airborne allergens or plicatic acid-HSA conjugate is not related to the type of asthmatic reaction. This fact is in accord with previous observations that patients with high levels of specific or total serum IgE did not show a greater prevalence of immediate reactions to western red cedar [3] or isocyanates [20].

Finally, subjects with an isolated immediate reaction differed from subjects with an isolated late reaction only with regard to the degree of non-specific bronchial hyperresponsiveness to methacholine. This difference was not previously reported and may be related to the fact that a late reaction is associated with an increase in bronchial hyperresponsiveness [21-23]. There are major differences between immediate and late reactions. Immediate reaction is a short-term airway response, which develops within a few minutes after the challenge and with recovery usually in 1 hr, while the late reaction is a more prolonged response, which begins 2-8 hr after the challenge and may persist for hours and sometimes days [24]. An immediate reaction is inhibited by previous administration of cromoglycate but not by steroids, while a late reaction is completely inhibited by steroids and partially by cromoglycate [24]. Late reactions, but not immediate reactions, induce an increase in non-specific bronchial hyperresponsiveness [21-23]. Further studies are required to look for a different role of chemical mediators and a different involvement of bronchial autonomic control in the different patterns of specific airway response.

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