American Journal of Industrial Medicine 25:13–18 (1994)

Mechanism of Occupational Asthma Due to Western Red Cedar (*Thuja plicata*)

Moira Chan-Yeung, MB, FRCPC, FRCP

Occupational asthma due to Western red cedar is the most common form of occupational asthma in the Pacific Northwest and affects 4–13.5% of the exposed population. It has been shown to be caused by plicatic acid, a low molecular weight compound present uniquely in the wood. The mechanism of asthma induced by plicatic acid is not known, as specific IgG antibodies were found only in about 20% of patients. Sera from patients with red cedar asthma failed to passively sensitize human lung fragments of human basophils. Basophils from patients with this disease released histamine when challenged directly with plicatic acid in a specific manner. Immunologic mechanisms other than Type I hypersensitivity reaction are likely to be involved. © 1994 Wiley-Liss, Inc.

Key words: plicatic acid, wood exposure, inhalation, organic dusts, occupational asthma

INTRODUCTION

Occupational asthma due to Western red cedar is a common occupational lung disease in the Pacific Northwest. In British Columbia, it accounts for 70% of all the compensation claims for occupational asthma [Workers' Compensation Board, 1991]. Western red cedar is used heavily for both indoor and outdoor construction because of its durability. It is different from other wood in its high content of chemicals in the extract of the wood. Some of these chemicals are fungicides.

Table I shows the volatile and nonvolatile components [Gardner, 1963]. Plicatic acid constitutes about 40% of the nonvolatile components. It has a molecular weight of 440 daltons; its structural formula is shown in Figure 1. Early studies demonstrated that patients who reacted on inhalation challenge tests to a crude extract of Western red cedar did not react to the extract after it had been dialyzed to remove water-soluble low molecular weight compounds. On the other hand, the removal of the volatile components did not remove the asthma-inducing property of the red cedar extract. When the patients were challenged with plicatic acid, they reacted with bronchoconstriction in the same way as with the crude red cedar extract, these results indi-

The University of British Columbia, Department of Medicine, Vancouver General Hospital, Vancouver, British Columbia, Canada.
Address reprint requests to Dr. Moira C.-Yeung, The University of British Columbia, Department of Medicine, Vancouver General Hospital, 2775 Heather Street, Vancouver, British Columbia V5Z 3J5, Canada.
Accepted for publication March 15, 1993.

© 1994 Wiley-Liss, Inc.

TABLE I. Composition of Western Red Cedar Extract

Volatile components
Methyl thujate
Thujic acid
Tropolones
β-thujaplicinol
y-thujaplicin
β-thujaplicin
α-thujaplicin
β-dolabrin
Nazukone
Carvacrol methyl ether
Nonvolatile components (water soluble)
Phenolic fraction
Plicatic acid
Plicatin
Thujaplicatin
Thujaplicatin methyl ether
Other lignans
Nonphenolic fraction
Pectic acid
Starch
Hemicellulose
Arabinase
Simple sugars

Data from Barton and MacDonald [1971].

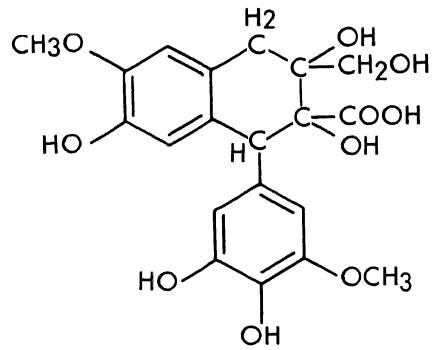

Fig. 1. Structural formula of plicatic acid.

cating that plicatic acid is the compound in red cedar that is responsible for asthma. Patients with nonoccupational asthma and without history of exposure to red cedar dust did not react on inhalation challenge test to plicatic acid, suggesting that the reaction is a specific one [Frew et al., 1992b].

TYPES OF ASTHMATIC REACTION INDUCED BY PLICATIC ACID

Inhalation challenge tests with an extract of western red cedar or plicatic acid induce three types of asthmatic reaction: isolated immediate, isolated late, and bi-

phasic or continuous reaction. Systemic reaction or alveolar reaction has not been observed [Chan-Yeung et al., 1973]. Unlike occupational asthma due to high molecular weight compounds, the proportion of patients with late asthmatic reaction is high (89%), either as isolated late or as part of a dual reaction [Chan-Yeung et al., 1982].

PATHOGENIC MECHANISM OF ASTHMA INDUCED BY PLICATIC ACID

Inhalation challenge tests with high molecular weight allergens induce isolated immediate and dual asthmatic reactions but not isolated late asthmatic reaction. It is well established that these allergens induce asthma by producing specific IgE antibodies. There is now convincing evidence that both the immediate and the late reactions are the results of an allergen-IgE antibodies reaction [Kaliner, 1984]. The immediate asthmatic reaction is likely to be due to chemical mediators, such as histamine, released during the allergic reaction. The late asthmatic reaction is the result of the late-phase allergic reaction associated with airways inflammation.

The pathogenic mechanism of asthma induced by plicatic acid is not clear. The clinical picture of red cedar asthma is one of allergic disease. There is a latent period between the onset of exposure and the onset of symptoms. Exposure to a small amount of red cedar dust can trigger an attack of asthma in sensitized subjects. However, skin tests with the crude extract of western red cedar and with plicatic acid were negative in patients [Chan-Yeung et al., 1973].

Plicatic acid can be conjugated to human serum albumin (HSA) to form an allergen. Using this conjugate as antigen, specific IgE antibodies can be found by RAST method in about 20% of the patients proven by inhalation challenge tests [Tse et al., 1982]. Moreover, the majority of the patients are non-atopic subjects, thus raising the question whether Type 1 allergic reaction is responsible for the pathogenesis.

Bronchoalveolar lavage studies of patients with red cedar asthma, before and during immediate asthmatic reaction, showed that there was release of inflammatory mediators, including histamine, prostaglandin D_2, leukotriene E_4 and thromboxane B_2, into the bronchoalveolar lavage fluid, suggesting mast cells were activated during the immediate reaction [Chan-Yeung et al., 1989]. Lam et al. [1987] examined the sequence of cellular and protein changes after late asthmatic reaction induced by plicatic acid in 44 patients with red cedar asthma by bronchoalveolar lavage, and the results were compared with 35 normal subjects. The late asthmatic reaction was found to be associated with an increase in eosinophils and albumin in the lavage fluid, and an increase in the sloughing of bronchial epithelial cells. Although there was a slight increase in neutrophils 48 hours after challenge, neutrophil infiltration was not a prominent feature earlier. Bronchial biopsies were carried out in three of the patients 24 hours after inhalation tests. The major findings were denudation of the bronchial epithelium, a thickened basement membrane, and infiltration of eosinophils in the bronchial submucosa. The finding of release of inflammatory mediators during the immediate asthmatic reaction and the presence of airways inflammation during the late asthmatic reaction are similar to patients with asthma induced by high molecular weight allergens.

DO SPECIFIC IgE ANTIBODIES PLAY A ROLE IN RED CEDAR ASTHMA?

In vitro, plicatic acid and plicatic acid-human serum albumin were found to induce histamine release from basophils, bronchoalveolar lavage cells, and bronchial biopsies of patients with red cedar asthma. Plicatic acid released histamine from basophils and bronchoalveolar lavage cells from 2/7 normal subjects but not from atopic asthmatics [Frew et al., 1992a]. The release of histamine from some normal subjects raised the possibility that plicatic acid may have both specific and nonspecific actions on human basophils and mast cells.

To assess whether low levels of specific IgE antibodies might account for histamine release in red cedar asthma, a series of passive sensitization studies were conducted with serum from patients with red cedar asthma. Human lung fragments passively sensitized with serum from red cedar asthma patients released 11.1% of their histamine content when challenged with plicatic acid, compared to 7.2% release when serum from non-atopic subjects was used. Lung fragments sensitized with serum from atopic subjects also gave a mean 11.1% histamine release when challenged with plicatic acid [Frew et al., 1992a].

Lactate-stripped human basophils were also passively sensitized with serum from patients with red cedar asthma. The findings were similar to human lung fragments. There was no difference between the serum of red cedar asthma patients and the serum of atopic subjects in their ability to transfer sensitivity to plicatic acid. Finally, basophils from patients with red cedar asthma were desensitized with anti-IgE in the absence of calcium and then challenged with plicatic acid or plicatic acid-HSA conjugate [Frew et al., 1992a]. While this desensitization protocol reduced the responsiveness of basophils from atopic subjects to challenge with grass pollen or with anti-IgE, there was only a limited effect upon basophil response to plicatic acid or plicatic acid-HSA. The above findings confirmed that specific IgE antibodies to plicatic acid-HSA conjugate cannot be responsible for release in patients with red cedar asthma.

OTHER IMMUNOLOGICAL MECHANISM IN RED CEDAR ASTHMA

It is quite possible that other immunological mechanisms may be involved in red cedar asthma. It is now generally accepted that T4 lymphocytes, after activation by specific antigen, elaborate a wide variety of lymphokines, some of which are directly implicated in the regulation of IgE synthesis [Tada, 1975]. In addition, T-lymphocyte products have the capacity to orchestrate the accumulation and activation of specific granulocyte effector cells at mucosal surfaces [Gonzales et al., 1987]. Changes in T-lymphocyte subsets in bronchoalveolar lavage fluid and peripheral blood following allergen challenge have been studied. A selective increase in CD4+ cells in bronchoalveolar fluid was observed 48 hours after challenge. In the peripheral blood, a decrease in CD4+ cells was found, suggesting selective recruitment of CD4+ T-lymphocytes in the lung during the late asthmatic reaction [Gerblich et al., 1984]. These observations suggest that lymphocytes play a role in the pathogenesis of asthma. Further studies are necessary to delineate the role of lymphocytes in the pathogenesis of red cedar asthma.

ANIMAL STUDY

Both guinea pigs and rabbits can be sensitized by the parenteral route to PA-HSA. High titers of specific IgG1 antibodies were produced in guinea pigs. Intravenous administration of plicatic acid to sensitized animals induced rapid shallow breathing and an increase in airway resistance immediately. Inhalation challenge with plicatic acid, however, failed to induce similar changes. In animals, plicatic acid conjugated to human serum albumin is immunogenic [Chan et al., 1987]. Unfortunately, this animal model does not reflect the human model of red cedar asthma, since the animals were sensitized by parenteral route rather than the inhalant route, and the conjugate, rather than the hapten, was used for sensitization.

PREVALENCE OF RED CEDAR ASTHMA

The prevalence of red cedar asthma in exposed workers varies from 4.1% to 13.5% [Ishizaka et al., 1973; Brooks et al., 1981; Chan-Yeung et al., 1986]. In a study by Chan-Yeung and Desjardins [1992], the prevalence of red cedar asthma determined by inhalation challenge test was 1.7% in a cedar sawmill of 350 workers. During the subsequent 6 years, six workers developed the disease at a rate of one per year, giving an incidence of 0.3% per year. The dust level in this sawmill was low. Very few samples collected by personal sampling were above 2 mg/m^3.

The prevalence of red cedar asthma in exposed workers is dependent on the level of exposure. The higher the level of exposure, the higher the prevalence of red cedar asthma. This has been demonstrated in two separate studies [Brooks et al., 1981; Chan-Yeung et al., 1986]. Given the same degree of exposure, only a small proportion of workers develop the disease. Predisposing host factors are important. Unfortunately, very little is known about this area. Atopy is not an important host factor in red cedar asthma, as the majority of patients with red cedar asthma are non-atopic subjects [Chan-Yeung et al., 1982]. The proportion of atopic subjects among patients with red cedar asthma is the same as those in the general population. Smoking is not a predisposing factor, as in asthma, due to large molecular weight allergens. On the contrary, the majority of patients with red cedar asthma are non-smokers [Chan-Yeung et al., 1982].

Nonspecific bronchial hyperresponsiveness is unlikely to be a predisposing host factor, as workers who developed red cedar asthma did not have nonspecific bronchial hyperresponsiveness before the development of the disease [Chan-Yeung and Desjardins, 1992]. Other predisposing factors have yet to be determined.

RED CEDAR ASTHMA AS A MODEL TO STUDY NON-ATOPIC ASTHMA

Occupational asthma is an excellent model to study the pathogenesis and the natural history of asthma. This is due to the fact that the agent responsible for asthma is known. Workers entering the high risk industry can be examined for various host factors and followed up regularly for the development of symptoms. Those who develop the disease can be removed from exposure and observed for the progression or regression of the disease. This is an ideal experiment that can be conducted on

humans in a working environment. Since red cedar asthma affects mostly non-atopic subjects, it is also an excellent model for studying adult onset asthma.

REFERENCES

Barton GM and MacDonald BF (1971): Chemistry and utilization of Western red cedar. Department of Fisheries and Forestry Publication No. 1023, Canadian Forestry Service, Ottawa, p 29.

Brooks SM, Edwards JJ, Apol A, Edwards FH (1981): An epidemiologic study of workers exposed to Western red cedar and other wood dust. Chest 80:30–32.

Chan H, Tse KS, Oostdam JV, Moreno R, Pare P, Chan-Yeung M (1987): A rabbit model of hypersensitivity to plicatic acid, the agent responsible for red cedar asthma. J Allergy Clin Immunol 79:762–767.

Chan-Yeung M, Desjardins A (1992): Non-specific bronchial hyperresponsiveness and dust exposure in patients with asthma due to Western red cedar—Serial observations before development of symptoms. Am Rev Respir Dis 146:1606–1609.

Chan-Yeung M, Barton G, Maclean L, Grzybowski S (1973): Occupational asthma and rhinitis due to Western red cedar (*Thuja plicata*). Am Rev Respir Dis 108:1094–1102.

Chan-Yeung M, Lam S, Koerner S (1982): Clinical features and natural history of occupational asthma due to Western red cedar (*Thuja plicata*). Am J Med 72:411–415.

Chan-Yeung M, Vedal S, Kus J, Maclean L, Enarson D, Tse KS (1986): Symptoms and pulmonary function in workers related to duration of employment and dust exposure. Arch Environ Health 41:179–183.

Chan-Yeung M, Chan H, Salari H, Lam S (1989): Histamine and leukotrienes release in bronchial fluid during plicatic acid induced bronchoconstriction. J Allergy Clin Immunol 84:762–768.

Frew A, Chan H, Lam S, Chan-Yeung M (1992a): Plicatic acid indices histamine release from bronchial mast cells and basophils of patients with Western red cedar asthma. Am Rev Respir Dis 145:A21.

Frew A, Chan H, Chan-Yeung M (1992b): Does specific IgE play any role in asthma due to Western red cedar? Am Rev Respir Dis 145:A21.

Gardner JA (1963): "Chemistry and Utilization of Western Red Cedar." Dept of Forestry Publication No. 1023, Ottawa, Canada: Department of Forestry.

Gerblich AA, Campbell A, Schuyler M (1984): Changes in T-lymphocyte subpopulations after antigen bronchial provocation in asthma. N Engl J Med 310:1349.

Gonzales MC, Diaz P, Gallequillos FR, Ancic P, Cromwell A, Kay B (1987): Allergen-induced recruitment of bronchoalveolar helper (OKT4) and suppressor (OKT8) T cells in asthma. Am Rev Respir Dis 136:600–604.

Ishizaka T, Shida T, Miyamoto T, Matsumara Y, Mizuno K, Tomaru M (1973): Occupational asthma from Western red cedar dust in furniture factory workers. J Occup Med 15:580–585.

Kaliner M (1984): Hypothesis on the contribution of late phase allergic responses to the understanding and treating of allergic diseases. J Allergy Clin Immunol 73:311–315.

Lam S, LeRiche J, Phillips D, Chan-Yeung M (1987): Cellular and protein changes in bronchial lavage fluid after late asthmatic reaction in patients with red cedar asthma. J Allergy Clin Immunol 80:44–50.

Tada T (1975): Regulation of reaginic antibody formation in animals. Prog Allergy 19:122–194.

Tse KS, Chan H, Chan-Yeung M (1982): Specific IgE antibodies in patients with occupational asthma due to Western red cedar (*Thuja plicata*). Clin Allergy 12:249–258.

Workers' Compensation Board of British Columbia (1991): "Occupational Injury and Diseases in British Columbia." Vancouver, BC: Workers Compensation Board of British Columbia.