

Recurrent nocturnal asthma after bronchoprovocation with Western Red Cedar sawdust: association with acute increase in non-allergic bronchial responsiveness

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Summary

Recurrent nocturnal asthma following a single exposure to Western Red Cedar sawdust was documented by measurements of peak flow rates in two sensitized subjects. The nocturnal asthma followed a dual asthmatic response in the first subject and a late (non-immediate) asthmatic response in the second. Both subjects developed a 10-fold reduction in the dose of histamine required to decrease the FEV₁ by 20%. This cedar-induced increase in non-specific bronchial reactivity was maximal at the time of the recurrent nocturnal asthma, and persisted after nocturnal asthma had ceased and after FEV₁ had returned to normal. We hypothesize that the enhanced non-specific bronchial reactivity which occurs following late asthmatic responses to bronchial challenge is the cause of recurrent nocturnal asthma following single exposure to a sensitizing agent.

Introduction

Recurrent nocturnal asthma has recently been observed to occur in sensitive subjects following single brief exposures to allergens (Davies, Green & Schofield, 1976; Newman Taylor *et al.*, 1979), isocyanate (Siracusa, Curradi & Abbritti, 1978), and Western Red Cedar (*Thuja plicata*) sawdust (Gandevia & Milne, 1970). Acute enhancement of bronchial responsiveness to histamine or methacholine has also been demonstrated following single brief exposures to allergen (Cockcroft *et al.*, 1977b; Cartier *et al.*, 1982; Bleecker, Norman & Mason, 1982), isocyanate (Cockcroft & Mink, 1979b), and Western Red Cedar sawdust (Cockcroft, Cotton & Mink, 1979a; Lam, Wong & Yeung, 1979; Hamilton *et al.*, 1979). Although these two phenomena have not been reported together, it has been speculated that the increased non-specific bronchial reactivity may be the cause of the recurrent nocturnal asthma (Cartier *et al.*, 1982; Cockcroft, 1982a). We have recently investigated two occupational asthmatics who developed both increase in the level of bronchial reactivity to inhaled histamine and recurrent nocturnal asthma documented by peak flow measurements following bronchoprovocation in the laboratory with Western Red Cedar sawdust.

Case reports

Patient 1

A 50-year-old ex-smoking male carpenter presented with progressively severe dyspnoea and chest congestion of 4 years' duration related to exposure to sawdust of Western Red Cedar and of particle boards containing Western Red Cedar. He also complained of sneezing and nasal congestion after the same exposure. Symptoms were worse at night (following exposure) and had progressed to include chest symptoms on immediate exposure to all dusts and to cold air. Oxtriphylline 200 mg four times daily, salbutamol aerosol 200 µg as needed, and avoidance of Western Red Cedar sawdust in his new supervisory role resulted in satisfactory control of symptoms. He had a past history of allergic rhinitis (but no chest symptoms) on exposure to freshly cut grass. Physical examination was normal. Haemoglobin, white blood cell count, peripheral eosinophil count, chest radiograph and pulmonary function studies were normal. Serum IgE was 20 u/l (normal 0–75). Skin-prick testing with twenty-five common allergens and eight extracts of wood dusts* revealed 1–2-mm wheals to house dust and mixed tree, grass and weed pollens; wood dust tests were negative. A histamine inhalation test showed moderate non-specific bronchial hyperreactivity.

Patient 2

A 25-year-old non-smoking male roofer presented with nasal and conjunctival irritation, wheezing, and dyspnoea related to exposure to freshly cut Western Red Cedar shingles. Milder symptoms were now present on exposure to dust, smoke and cold air. Attacks of wheezing and dyspnoea had required numerous emergency-room visits, and one of these episodes was associated with a left-sided pneumothorax requiring chest tube drainage. Symptoms were reported to take between 4 and 6 weeks to resolve after exposure to Western Red Cedar had ceased. At the time of presentation, chest symptoms were well controlled with aerosol beclomethasone 100 µg three times daily and aerosol salbutamol 200 µg as needed and avoidance of Western Red Cedar. Physical examination was normal. Haemoglobin, white blood cell count, eosinophil count, chest radiograph and pulmonary function studies were normal. Serum IgE was 54 u/l. Allergy skin-prick tests with twenty-five common allergens and eight wood dust extracts* revealed only a 3-mm wheal to house dust. Histamine inhalation revealed mild non-specific bronchial hyperreactivity.

Special investigations

Bronchoprovocation with wood dusts

Bronchoprovocation testing with sawdusts was done in a simulated work environment (Pepys & Hutchcroft, 1975). Sawdust was generated in a closed chamber (150 × 180 × 240 cm) using a commercial heavy-duty belt sander and planks of pure

* Allergens used for skin-prick tests included *Alternaria* 1/20, *Cladosporium* 1/20, *Helminthosporium* 1/20, *Aspergillus* mix 1/20, house dust 1/5, grain dust 1/20, wheat dust 1/20, feathers 1/20, horse dander 1/125, cow dander 1/20, box elder pollen 25 000 nu/ml, birch pollen 25 000 nu/ml, poplar pollen 25 000 nu/ml, willow pollen 25 000 nu/ml (Bencard Allergy Service, Weston, Ontario), dog hair and dander 1/10, cat hair 1/10, egg 1/20, cow's milk 1/20, peanut 1/10, shellfish mix 1/10, *D. farinae* 1/50, ragweed 1/20, mixed tree pollen 1/20, mixed weed pollen 1/20, mixed grass pollen 1/20, spruce dust 1/10, cedar/juniper dust 1/10, fir/hemlock dust 1/10, oak dust 1/10, walnut dust 1/10, maple dust 1/10, mahogany dust 1/10, and redwood dust 1/10 (Hollister Stier Laboratories, Mississauga, Ontario).

spruce and cedar. At the time of testing patients were stable and had no exposure to cedar or relevant allergens (patient 1) for several weeks. Patient 2 had discontinued beclomethasone 3 weeks earlier. Both patients had normal FEV₁ on all test days and required inhaled salbutamol infrequently (less than daily), but none for more than 8 hr prior to test days. Patient 1 was exposed to spruce sawdust as a control for 5, 10, and 20 min with 10 min between exposures. The forced expired volume in 1 sec (FEV₁) was measured in duplicate at time 0, 10 min after each exposure, and 10, 20, 30, 40, 50, 60, 90, 120, 180, 240, 300, 360, and 420 min after the last exposure. The next day, exposure was repeated with Western Red Cedar sawdust for only 5 min; FEV₁ was measured as on the control day. On 3 consecutive days patient 2 was exposed to spruce (2, 4 and 8 min), cedar (2, 4, and 8 min) and cedar again (4, 8 and 16 min) with time between challenges and FEV₁ measurements as for patient 1.

Histamine inhalation tests

Non-specific bronchial reactivity to inhaled histamine was measured as previously described (Cockcroft *et al.*, 1977a). Aerosols were generated with a Wright nebulizer operated with an airflow rate of 7.5 l/min delivering an output of 0.13 ml/min and a particle size mass median diameter of 1 µm. After a control inhalation of 0.9% saline, doubling concentrations of histamine from 0.03 to 8.0 mg/ml were inhaled for 2 min at 5-min intervals. The FEV₁ was initially measured in triplicate and repeated 30 and 90 sec after each inhalation. The % reduction was calculated from the lowest post-saline FEV₁ to the lowest post-histamine FEV₁ and the test discontinued after the FEV₁ had fallen by greater than 20%. The histamine provocation concentration producing a 20% FEV₁ fall (PC₂₀) was calculated from the dose-response curve.

The histamine PC₂₀ was measured eight times in patient 1 and ten times in patient 2. In patient 1, PC₂₀ was determined the day before spruce exposure, 8 hr after spruce exposure, and 8 hr, 1, 2, 5, 8, and 14 days after cedar challenge. In patient 2, PC₂₀ was determined 3 days before challenges, 8 hr after each of the three challenges, and 1, 2, 5, 8, 15, and 35 days after the final challenge.

Peak flow rates

Peak flow rates (PFR) were measured in triplicate with a Wright Mini Peak Flow Meter four times daily and at night if dyspnoea and wheezing awoke the patient. Patient 1 measured PFR in this fashion for 14 days after cedar challenge and patient 2 measured PFR from 2 days prior to control (spruce) challenge to 8 days after completion of challenges. The highest value at each time was recorded.

Results

Wood dust bronchoprovocation:

Results of bronchoprovocation studies are shown in Figure 1. Patient 1 had no change in FEV₁ 10 min after the 5- and 10-min spruce exposure. An 18% FEV₁ fall after the 20-min spruce exposure reversed in less than 30 min (to a 6% increase) and was interpreted as an irritant response. There was no late FEV₁ fall after spruce. The 5-min cedar sawdust exposure resulted in a dual asthmatic response with a 40% FEV₁ fall 40 min after exposure, a partial spontaneous recovery (to -14%), and a late 48% FEV₁ fall at 8 hr. Patient 2 had less than ±5% variability in FEV₁ at all times following the cumulative 14-min spruce exposure on the first day and the cumulative 14-min cedar

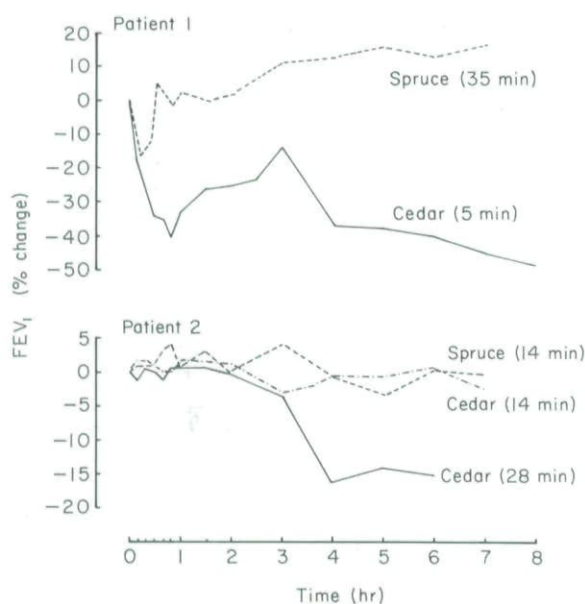


Fig. 1. Bronchoprovocation tests with spruce (control) and Western Red Cedar sawdust in the two patients. FEV_1 (% change) is shown on the vertical axis and time (hr) on the horizontal axis. Time 0 is immediately prior to exposure; the times on the horizontal axis are time following completion of the final exposure (see text).

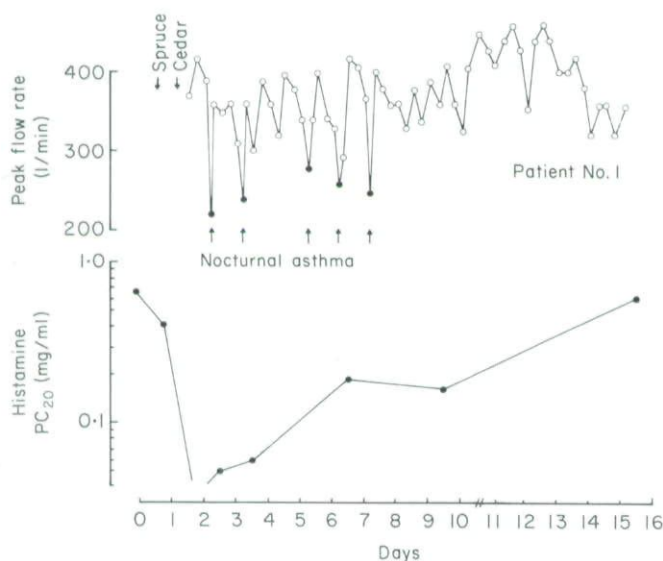


Fig. 2. Peak flow rates (PFR) and bronchial responsiveness to histamine following bronchoprovocation with Western Red Cedar in patient 1. PFR l/min is on the vertical axis of the top graph and histamine PC_{20} (mg/ml) on the vertical axis of the bottom graph, with time (days) on the horizontal axis. Bronchoprovocation was done with spruce sawdust on day 0 and Western Red Cedar sawdust on day 1. Nocturnal asthma occurred on 5 of the 6 nights following cedar challenge.

exposure on the second day. However following the 28-min cumulative cedar challenge, an isolated late asthmatic response was evident with a 16% FEV₁ fall 5–7 hr after exposure.

Histamine inhalation tests

Changes in histamine PC₂₀ in patient 1 are shown in Figure 2. Moderately increased responsiveness to a similar degree was demonstrated in the control and following spruce exposure. Eight hours after cedar exposure, PC₂₀ was not measurable because of a response to diluent. The next day the PC₂₀ was reduced 10-fold below control measurements when baseline FEV₁ was 33% below control values, and was likewise reduced 2 days after exposure, when baseline FEV₁ was within 10% of control values. The PC₂₀ returned to control levels over 2 weeks.

Changes in histamine PC₂₀ in patient 2 are shown in Figure 3. Baseline FEV₁ was within 10% of control for all tests except 8 hr after cedar when it was reduced by 16%. There was no change in bronchial responsiveness (in the mild range) following spruce, a 3-fold reduction 8 hr after the 14-min cedar exposure, and a progressive reduction in PC₂₀ for 2 days after 28-min cedar exposure, which returned towards the control value over 5 weeks.

Peak flow rates

Values for PFR in relation to histamine PC₂₀ are shown in Figures 2 and 3 for patient 1 and patient 2 respectively. Patient 1 developed recurrent nocturnal asthma with PFR less than 300 l/min on 5 of 6 nights following cedar exposure; on the night without asthma he used 200 µg salbutamol prophylactically at bedtime. He had not recorded

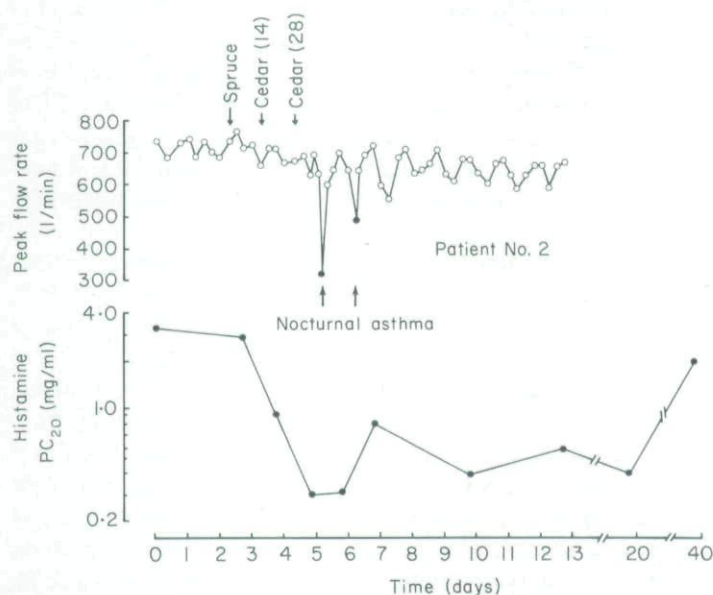


Fig. 3. PFR and histamine PC₂₀ following bronchoprovocation with Western Red Cedar sawdust in patient 2. The axes are the same as for Fig. 2. The patient was challenged with spruce for 14 min on day 2, and Western Red Cedar for 14 min on day 3 and for 28 min on day 4. Nocturnal asthma occurred for 2 nights following cedar challenge.

nocturnal asthma for several weeks before exposure, nor for the period of time from 7 to 14 days post cedar challenge. Patient 2 developed nocturnal asthma for 2 nights after the second (28-min cumulative) cedar exposure with associated falls in peak flow rate. In both subjects, nocturnal asthma occurred during the period of maximal reduction in histamine PC₂₀.

Discussion

In these two patients, we have documented the appearance of recurrent nocturnal asthma due to single exposures to Western Red Cedar sawdust. The recurrent nocturnal asthma occurred in both subjects following a late (or non-immediate) asthmatic response, and was associated with significant increases in bronchial responsiveness to histamine.

The important and common factor which appears to link recurrent nocturnal asthma and induced increases in non-specific bronchial reactivity is the late or non-immediate asthmatic response occurring generally 3–8 hr after challenge. Virtually all reported instances of increased non-specific bronchial reactivity following specific bronchoprovocation with allergen, Western Red Cedar, and low mol.wt sensitizing chemicals, have occurred following late asthmatic responses (Cockcroft *et al.*, 1977b; Vallières *et al.*, 1977; Cockcroft, Cotton & Mink, 1979a; Lam, Wong & Yeung, 1979; Hamilton *et al.*, 1979; Cockcroft & Mink, 1979b; Cockcroft *et al.*, 1980; Cartier *et al.*, 1982). A review of twenty-five allergen bronchoprovocation tests from the studies of Cockcroft *et al.*, (1977b) and Cartier *et al.*, (1982) would suggest that increased bronchial responsiveness to histamine appears virtually always following a late asthmatic response, and persists after even sensitive measurements of airflow obstruction have returned to baseline (Cartier *et al.*, 1982). Cartier *et al.*, (1982) have also shown that the severity of the late asthmatic response correlates well with both the magnitude and the duration of the reduction in histamine PC₂₀. The majority of cases of recurrent nocturnal asthma following single exposure to a sensitizing agent also appear to occur following late asthmatic responses (Davies, Green & Schofield, 1976; Siracusa, Curradi & Abbritti, 1978; Newman Taylor *et al.*, 1979). Thus it appears that late asthmatic responses following bronchoprovocation with a sensitizing agent may be invariably followed by increased non-specific bronchial reactivity, and occasionally by recurrent nocturnal asthma.

It may be logical, therefore, to speculate that the increased non-specific bronchial reactivity is the cause of the recurrent nocturnal asthma (Cartier *et al.*, 1982; Cockcroft, 1982a). The degree of non-specific bronchial reactivity correlates well with many measurements of the severity of asthma including symptoms (Makino, 1966; Muranaka *et al.*, 1974), medication requirements (Cockcroft *et al.*, 1977a; Juniper, Frith & Hargreave, 1981), exercise-induced asthma (Eggleston, 1979; Anderton *et al.*, 1979), and cold-air-induced asthma (O'Byrne *et al.*, 1982). Likewise, nocturnal symptoms are recognized as common in asthma and relate to reduced night-time flow rates (Clark & Hetzel, 1977) and thus may be more common and more pronounced as asthma becomes more severe. Reduction and variability in daily peak flow rates, such as those reported by Clark & Hetzel (1977), are also more pronounced as non-specific bronchial reactivity increases (Ryan, Latimer & Hargreave, 1982). Thus it appears reasonable to speculate that recurrent nocturnal asthma is another manifestation of the induced increases in airways hyperreactivity.

The mechanisms underlying the late asthmatic response, the induced increases in

non-specific bronchial reactivity, and the consequent episodes of recurrent nocturnal asthma, although likely interrelated, remain obscure. The pathophysiology of the late response likely involves mucosal inflammation and secretions as well as smooth muscle contraction (Cartier *et al.*, 1982). Although increased bronchial responsiveness to histamine may in part relate to reduced airway calibre (Benson, 1975), recent studies by Cockcroft, Cotton & Mink (1979a) and Cartier *et al.*, (1982) have shown that the histamine PC₂₀ may remain substantially reduced even after sensitive measures of small airway calibre have returned to baseline. Thus reduced airway calibre alone cannot explain this phenomenon. Increased mucosal permeability follows allergen challenge in monkey (Boucher, Paré & Hogg, 1979) and may explain increased susceptibility to the effects of histamine; this hypothesis awaits testing in man. Increased irritant receptor sensitivity has been postulated as causing increased bronchial responsiveness to histamine following viral infections (Empey *et al.*, 1976). However, following allergen challenge, the similar changes in responsiveness to both histamine and methacholine (Cockcroft *et al.*, 1977b) and the failure to block such changes to histamine with atropine (Bleecker *et al.*, 1982) suggests afferent vagal pathways are not affected. Other possible mechanisms include altered autonomic nervous system function (Szentivanyi, 1968; Richardson & Bouchard, 1975; Miller, Fish & Patterson, 1977) and altered smooth muscle function (Stephens *et al.*, 1980).

The findings demonstrated by these two patients have major clinical relevance. Both the late asthmatic response and symptomatic increased non-specific bronchial reactivity are delayed and may be prolonged. For these reasons, relationship to the causative agent may be missed both by the patient and physician. A recognition and understanding of these responses to sensitizing agents should result in earlier detection of the aetiological agent, particularly in occupational asthma. This is particularly relevant as continued exposure to such agents may cause permanent symptomatic airways hyperreactivity (Lam, Wong & Yeung, 1979; Chan Yeung, Lam & Koener, 1982; Cockcroft, 1982b).

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