

Clinical and socio-professional fate of isocyanate-induced asthma

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Summary

Thirty-one patients with isocyanate-induced asthma were studied 6–54 months after diagnosis. Four had the same work conditions and unchanged or worse respiratory symptoms; seven had an alternative job or safer work conditions at the same work-place and suffered from mild to severe symptoms. The remaining twenty subjects were definitely removed from exposure; of these, ten (50%) remained symptomatic after being removed from exposure for an average of 19 months. Asymptomatic patients appeared to be younger and to have shorter durations of total and symptomatic exposures, while symptomatic patients were more reactive to acetylcholine at diagnosis. For patients removed from isocyanate exposure and for those re-employed at the same work-place, quality of the new work site seems to play a role in the evolution of isocyanate-induced asthma.

Introduction

When asthmatics whose asthma is caused by occupational agents are removed from further exposure to these agents, clinical and functional sequelae of their asthmatic condition may remain. Some question exists as to whether duration of exposure to the occupational agent and the patient's pulmonary status are prognostically important in determining outcome after removing the patient from further exposure. This appears to be the case for red cedar [1–3] and crab-induced asthma [4], but not for colophony [5] or TDI-induced asthma [6]. To collect additional data on these questions, the authors studied the outcome of removing patients with isocyanate-induced asthma from exposure to their sensitizer.

Subjects and methods

Thirty-one subjects with isocyanate-induced asthma were recalled 6–54 months after diagnosis; twenty of them were car spray-painters who used polyurethane paint, four

Table 1. Clinical features of thirty-one subjects with isocyanate-induced asthma at diagnosis

Age at diagnosis (years)	35.94 $\pm$ 2.99*
Smoking habits	
Non and ex-smokers	25 (81%)
Current smokers	6 (19%)
Atopy	9 (29%)
Previous history of asthma	1 (3%)
Duration of exposure before onset of symptoms (months)	35.63 $\pm$ 12.84
Duration of symptoms before diagnosis (months)	16.90 $\pm$ 4.98
Symptoms	
Rhinitis	6 (19%)
Wheeze	30 (97%)
Shortness of breath	30 (97%)
Cough	28 (90%)
Pulmonary function (% predicted)	
FEV ₁	96.98 $\pm$ 6.41
VC	100.55 $\pm$ 6.08
Acetylcholine inhalation test	
No. available	30 (97%)
No reaction	8 (27%)
FEV ₁ fall with 0.1 mg/ml	8 (27%)
FEV ₁ fall with 0.01 mg/ml	11 (36%)
FEV ₁ fall with 0.001 mg/ml	3 (10%)

* Mean $\pm$ s.e.m. or number (%).

manufactured polyurethane foam, four worked in the vicinity of engineering processes emitting various isocyanate compounds, two were cabinet makers who used polyurethane products for glue and varnish, and one used polyurethane foam for electrical insulation. Sixteen subjects had specific inhalation challenges at the hospital laboratory; one had work-related symptoms concurrent with specific IgE for HDI and MDI (RAST, Phadebas, Pharmacia, Sweden); and the rest had work-related symptoms, non-specific bronchial hyper-reactivity and patterns of peak expiratory flow rates, suggesting work-related asthma.

The study comprised both the administration of a questionnaire and pulmonary function testing.

In the questionnaire, information was obtained about the following: (i) work status since diagnosis: complete removal from exposure, alternative job at the same workplace, same work with improved ventilation, unchanged work conditions; (ii) interval since end of exposure or since re-employment; (iii) presence of symptoms such as wheezing at night and/or during the day either on exposure to isocyanates or to non-specific irritants (pollutants such as fumes or dusts and/or exercise/or cold air), attacks of wheezing provoked by upper respiratory tract infections, shortness of breath, rhinitis; (iv) requirement for medications and (v) smoking habits.

Pulmonary function testing

Pulmonary function testing assessed the following.

(1) Spirometry (FEV₁, VC) using a Cara spirometer (Gauthier, Paris, France). Reference values for FEV₁ and VC were these of the European Community for coal and steel [7].

(2) Bronchial reactivity to acetylcholine. Non-specific reactivity was measured by a semi-quantitative method: an aerosol of acetylcholine generated by an 'atomizer' nebulizer (output: 3 litre/min) was inhaled by the tidal breathing method for 3 min at successive concentrations (0.001, 0.01 and 0.1 mg/ml) until the maximum concentration was reached. Normal reactivity was defined as the absence of significant change in FEV₁ with the 0.1 mg/ml acetylcholine solution. Significant change in bronchial responsiveness between evaluations, done at the time of diagnosis and at follow-up, was defined either as a difference of 15% or more in magnitude of decline of FEV₁ with the same concentration of acetylcholine or as the need to use two different concentrations to obtain a 15% fall of FEV₁.

Information concerning symptoms, smoking habits, immediate cutaneous reactions to fourteen commonly inhaled allergens and lung function tests at the time of diagnosis was also available.

Analysis

The non-parametric Mann Whitney *U*-test, and the Pearson's correlation coefficient test were used for statistical comparisons.

Results

Table 1 depicts the clinical features of the thirty-one patients at the time when they were still exposed to isocyanates. Isocyanates bronchial provocation tests were performed in sixteen subjects: two had an immediate-type reaction, three a late reaction and one a dual response; in ten subjects, the type of response was impossible to interpret as they received bronchodilator and corticosteroid medication soon after a large immediate-type response was observed.

Duration of symptomatic exposure, which means delay to accurate diagnosis, averaged 17 months (range 1–66 months).

At follow-up, four subjects were working under unchanged conditions (group 1), seven were re-employed at the same work-place (group 2) and twenty subjects were completely removed from exposure (group 3).

Table 2 depicts clinical and functional details of groups 1 and 2 at follow-up. All patients in group 1 were symptomatic and needed permanent medication. One patient described unchanged paroxysmal symptoms after 6 months and two complained of progressive worsening after 6 and 10 months of persistent exposure. One patient re-evaluated after 30 months had unchanged paroxysmal symptoms over 2 years, followed by persistent shortness of breath. Bronchial response to acetylcholine (Fig. 1), FEV₁, and VC worsened or remained unchanged. In group 2, four patients had an alternative job at the same work-place and only unusual contact with isocyanates. Three of them improved clinically; one patient complained of persistent attacks of wheezing she thought were due to pollutants and the possibility of isocyanates in her new work environment. All four patients complained of shortness of breath following exposure to non-specific irritants, especially fumes. Spirometry values were improved

Table 2. Follow-up: clinical and functional details in groups 1 and 2

	Group 1 (n=4)	Group 2 (n=7)		
M:F	4:4	6:7		
Mean age (years)	48.8	37.6		
Rhinitis				
Initial	2	1		
Follow-up	2	2		
Atopy	1	1		
Previous history of asthma	1	—		
Smoking habits				
Non and ex-smokers	2	6		
Current smokers	2	1		
		AJ*(n=4)	SWC†(n=3)	
Duration of follow-up (months)	6-30	9-54	12-48	
Mean value	13	39	30	
Respiratory symptoms on follow-up				
Recurrent attacks of wheezing	4	1	3	
Rare attacks of wheezing	—	3	—	
Permanent shortness of breath	1	—	2	
Shortness of breath on irritants	4	4	3	
Need for permanent medication	4	1	3	
Mean FEV ₁ (% predicted)				
Initial	96	102	102	
Follow-up	86.25	116.25	99	
Mean VC (% predicted)				
Initial	102.50	100.75	112	
Follow-up	96.25	121.50	110	

* AJ: alternative job.

† SWC: safer work conditions.

in all four patients. Bronchial reactivity was normal or improved in three patients and unchanged in one (Fig. 1). Three patients did the same job but with improved conditions (e.g. efficient masks, adequate ventilation); all of them complained of recurrent episodes of wheezing and required permanent medication, although one was clinically improved; spirometry results remained unchanged for him but worsened for the other two.

Group 3 consisted of twenty subjects completely removed from isocyanate exposure. Although every patient answered the follow-up questionnaire, six refused lung function tests because they were asymptomatic. In addition to these, another four were symptom-free. Symptomatic patients had been working under changed conditions for a shorter time than symptom-free individuals ($P < 0.05$). Four patients reported rare attacks of wheezing during the year, provoked by bronchitis or pollution, and mild shortness of breath on exposure to fumes, cold air or humidity. Six patients had more severe symptoms (dyspnoea on exertion and/or frequent attacks of wheezing), two had permanent airway obstruction and three needed permanent

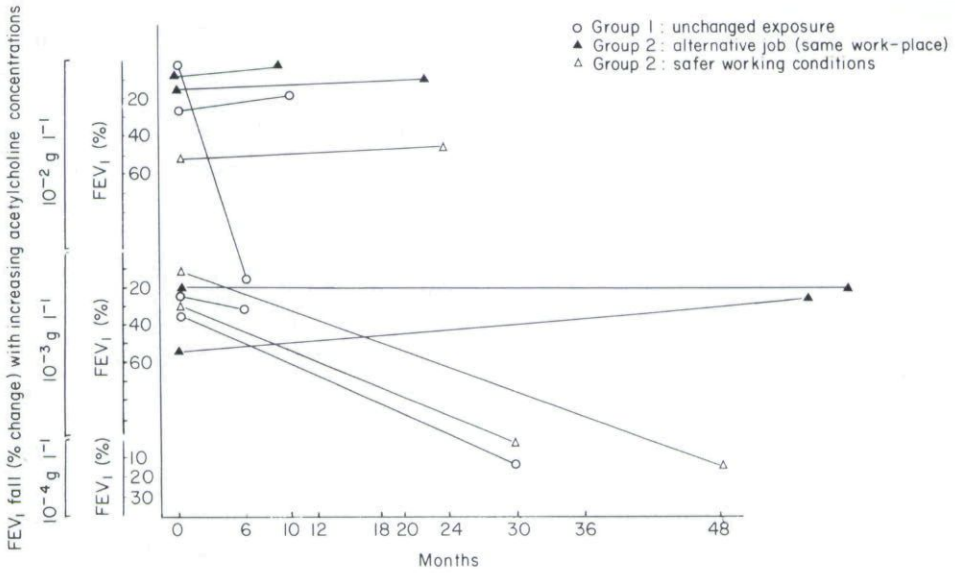


Fig. 1. Evolution of bronchial reactivity in groups 1 and 2.

Table 3. Follow-up: clinical and functional details in group 3

	Symptomatic subjects (n = 10)	Asymptomatic subjects (n = 10)
M:F	8:10	9:10
Mean age (years)	42.70 (P < 0.01)	34.20
Rhinitis		
Initial	2	2
Follow-up	1	—
Atopy	4	3
Previous history of asthma	—	—
Smoking habits		
Non and ex-smokers	7	7
Current smokers	3	3
Mean duration of total exposure (months)	57.20 (P < 0.025)	38.72
Mean duration of symptomatic exposure (months)	19.50 (P < 0.05)	7.80
Mean duration since exposure (months)	19.00 (P < 0.05)	35.00
Mean FEV ₁ (% predicted)		
Initial	93.00	98.40
Follow-up	97.10	107.00 (n = 4)
Mean VC (% predicted)		
Initial	98.40	99.40
Follow-up	103.20	116.25 (n = 4)

medication. In three patients, persistence of symptoms was directly related to exposure to dust or fumes in the new work-place. Although atopy occurred no more frequently in the symptomatic group (4/10) than in asymptomatic (3/10), atopic patients developed specific complications (e.g. pollinosis—one patient; atopic asthma—one patient). Asymptomatic patients were younger ($P < 0.01$), had a shorter duration of symptomatic exposure ($P < 0.05$) and a shorter duration of total exposure ($P < 0.025$). No link was found between age and duration of total exposure ($r = -0.0068$). The symptomatic patients were more reactive to acetylcholine at diagnosis ($P < 0.025$) (Fig. 2) but initial values of FEV₁ and VC were similar in the two groups. Figure 2 shows the evolution of bronchial reactivity in group 3. FEV₁ and VC in the symptomatic group at follow-up were not significantly different from initial values. In the asymptomatic group, lung function data were available for only four subjects and could not be used for statistical comparisons.

Discussion

The present study confirms and extends previous results about the evolution of occupational asthma. In agreement with Paggiaro *et al.* [6], we found that respiratory symptoms often persisted despite removal from exposure, and we agreed with Moller *et al.* [8] that bronchial hyper-responsiveness can last more than 4 years after cessation of exposure. Fifty per cent of these subjects remained symptomatic 19 months after cessation of exposure to isocyanates: six subjects (30%) remained seriously symptomatic, although all six described real clinical improvement, while four subjects complained of milder symptoms. We expect the shortness of breath manifested by these four patients to disappear with time, as was the case for the symptom-free group.

The patients in this study had fewer persistent symptoms than reported by Paggiaro *et al.* [6]. This may have occurred because when evaluating frequency of sequelae, asymptomatic patients were included who felt so well that they declined to lose working time by coming back to the laboratory for pulmonary function tests.

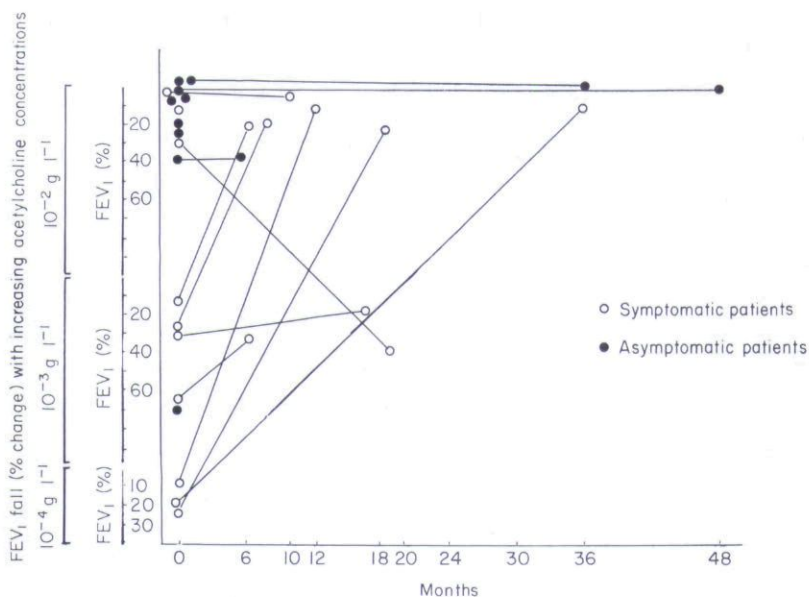


Fig. 2. Evolution of bronchial reactivity in Group 3.

As Chan-Yeung *et al.* [3] and Hudson *et al.* [4] have shown, the authors also found a relationship between persistence of symptoms after cessation of exposure and some of the patients' clinical features. Prognostic factors include duration of symptoms, length of exposure to the sensitizer and bronchial hyper-responsiveness at diagnosis. Age at diagnosis is also a prognostic factor independent from the total duration of exposure. Although not statistically significant, the quality of the new work-site (i.e. mean and threshold levels of non-specific pollutants there) seems to play a role in the evolution of occupational asthma. Our preliminary report [9] revealed no relationship between duration of exposure after onset of symptoms and sequelae: this seems to have been due to the fact that there was an insufficient number of subjects in that study.

One interesting observation was that although atopy does not appear to be more frequent in symptomatic patients, it may be responsible for specific complications; thus, it may represent an additional risk factor for respiratory sequelae.

Four patients did not alter their exposure and, despite medication, all remained symptomatic. The fact that one patient became suddenly worse after an additional 2 years' exposure suggests that persistent exposure will probably result in increased respiratory impairment sooner or later. The fact that these patients were older than others who changed their exposure by changing jobs highlights the difficulties inherent in finding new jobs for older workers.

Seven of the patients were re-employed at the same work-place. Those continuing the same work under safer conditions remained seriously symptomatic, although exposure to isocyanates was dramatically reduced.

Thus, following exposure to occupational sensitizers, even modest re-exposure, allows the allergic process to continue. In contrast, in former patients given new jobs in which the sensitizing agent was nearly always absent, excellent clinical and functional improvement was observed. Obviously, this is the therapeutic goal to follow.

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