

Mild Improvement in Symptoms and Pulmonary Function in a Long-Term Follow-Up of Patients with Toluene Diisocyanate-Induced Asthma

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Key Words

Occupational asthma · Bronchial hyperresponsiveness · Methacholine

Abstract

Background: Long-term follow-up of diisocyanate-induced occupational asthma has been occasionally reported. **Methods:** We studied the outcome of toluene diisocyanate (TDI)-induced asthma in 46 patients at diagnosis and after a follow-up of 11 ± 3.6 years. Symptoms, anti-asthma therapy, forced expiratory volume in 1 s (FEV₁) and bronchial hyperresponsiveness to methacholine were assessed. **Results:** A significant improvement in FEV₁ (% predicted) and PD20FEV₁ methacholine was observed at follow-up in comparison with diagnosis. Anti-asthma treatment was performed by 42% of patients at diagnosis and by 70% at follow-up. At the time of follow-up, 32 subjects had been removed from exposure for 6.0 ± 6.9 years, whereas 14 subjects continued to work with reduced exposure to TDI. There was a significant reduction in the prevalence of attacks of shortness of breath and dyspnoea at follow-up, but only in unexposed patients. PD20FEV₁ was significantly improved only in patients with a lower FEV₁ at diagnosis and in those who have ceased work. Logistic regression analysis, using different models with some independent variables, showed that there were no significant determinants of improvement in FEV₁ at follow-up,

while a shorter duration of symptoms before diagnosis was a significant predictor of improvement in PD20FEV₁ at follow-up. **Conclusions:** Asthma-like symptoms, bronchial hyperresponsiveness and airway obstruction improved, but did not normalize, after a long-term follow-up with cessation or reduction in TDI exposure, mainly in subjects with an early diagnosis of occupational asthma and in patients with a lower baseline FEV₁ no longer exposed to TDI.

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Introduction

Diisocyanates are among the most frequent causes of occupational asthma in many countries, but the precise pathogenesis of diisocyanate-induced asthma has not been clarified [1]. The outcome of toluene diisocyanate (TDI)-induced asthma has been extensively investigated [2], but only few studies included long-term follow-up patients with a diagnosis of TDI-induced asthma confirmed by a specific challenge test [3, 4]. In most studies, respiratory symptoms and airway hyperresponsiveness to methacholine persisted in the majority of asthmatic subjects removed from exposure to TDI [5], and earlier studies have shown that a considerable proportion of patients do not recover from occupational asthma [for a review, see ref. 6]. A more favourable prognosis was associated

with a better lung function, a lower degree of airway hyperresponsiveness to methacholine at diagnosis [4], and early removal from exposure after the onset of asthma [7, 8].

In this study, 46 patients with TDI-induced asthma were examined during a long-term follow-up to evaluate the clinical outcome of the disease and to assess the main determinants of the persistence of asthma symptoms and pulmonary function impairment.

Patients and Methods

Patients

Eighty-one patients with TDI-induced asthma were diagnosed in our unit during the period 1985–2000. At the time of diagnosis, all patients were asked for a detailed clinical and occupational history and underwent skin prick tests to common allergens as well as pulmonary function tests. Forced vital capacity and forced expiratory volume in 1 s (FEV₁) were obtained, and methacholine inhalation challenge was performed. The diagnosis of TDI-induced asthma was confirmed in all patients by a positive response to the specific inhalation challenge (SIC) in laboratory with TDI vapours.

The majority of workers studied ($n = 54$) were employed in furniture factories or carpentry plants. There were 61 males and 20 females included in the study. A small proportion of the patients were smokers and atopic. The average duration of exposure to TDI was 22.3 ± 13.34 years. Most of the subjects were hyper-reactive to methacholine and the SIC showed an early response in 36 patients, a late response in 23 patients and a dual response in 22 patients.

Follow-Up

Of the 81 patients, only 46 participated in the follow-up (average duration of follow-up 11 ± 3.6 years). These patients were asked for a detailed clinical and occupational history and underwent pulmonary function tests as well as methacholine inhalation challenge. Five of them did not perform the inhalation challenge with methacholine at follow-up because of airway obstruction, and 6 patients refused to perform methacholine challenge.

Methods

Respiratory symptoms (cough, wheeze, attacks of shortness of breath and dyspnoea) were assessed at baseline and follow-up as present (at least 2 symptoms/week in the last 4 weeks) or absent.

Spirometry was performed with a computerized water-sealed bell spirometer (Biomedin, Padua, Italy), following the standard recommendations [9].

Asthma severity was assessed according to GINA recommendations [10], including the frequency of symptoms in the last month, number of exacerbations in the last year, and FEV₁ level. In patients under pharmacological treatment, asthma severity assessment was corrected by the level of pharmacological treatment [10].

A bronchial provocative test with methacholine was performed when baseline FEV₁ was $\geq 70\%$ of the predicted value,

according to the method previously described [11]. Methacholine responsiveness was expressed as the cumulative dose producing a 20% FEV₁ fall from the baseline value (PD20FEV₁), and a PD20FEV₁ value < 1 mg was considered as a positive response.

SIC with TDI was performed in a 9 m³ exposure chamber, as previously described [11]. TDI atmosphere was generated by blowing air over the surface of 30 ml of TDI in a 250-ml glass washing bottle. The flow rate of air was controlled by a rotameter calibrated at a flow rate of 2 l/min. A fan in the chamber ensured adequate mixing and circulation. The concentration generated was measured by means of MDA model 7005 isocyanate detection equipment (MDA Scientific Inc., Glenview, Ill., USA). Each subject was observed through the window of the chamber; the duration of exposure was the same (30 min) for all subjects. FEV₁ was measured immediately before and after exposure to TDI, then hourly for 8 h.

Prick tests were performed with a panel of 11 common allergens including mites, pollens, moulds and animal danders. The results were evaluated after 20 min with measurements of the mean wheal diameter subtracting the negative control. The presence of a wheal ≥ 3 mm to one or more of the allergens was considered as evidence of atopy.

Statistical Analysis

Prevalence of respiratory symptoms are reported as percentages. FEV₁ is expressed as the mean (SD) and PD20FEV₁ methacholine as the geometric mean. Statistical significance of the unadjusted differences in prevalence of symptoms and bronchial hyperresponsiveness between groups in contingency tables was assessed by χ^2 analysis. A p value < 0.05 was considered significant, and a p value < 0.1 – 0.05 was considered suggestive of a trend.

Logistic regression was used to analyse the effects of potential factors (independent variables, like duration of symptoms, length of employment, removal from TDI exposure, baseline FEV₁ and PD20FEV₁) on the dependent variables (change in FEV₁ or PD20FEV₁ ratio between follow-up and baseline, separately). Improvement in FEV₁ at follow-up was expressed as a positive difference between FEV₁ % predicted at follow-up and at baseline, while improvement in PD20FEV₁ methacholine was expressed as a follow-up/baseline PD20FEV₁ ratio of > 1.5 (which was the median value of the distribution of this ratio among the single patients). The results are given in terms of odds ratios with 95% confidence intervals. Dependent and independent categorical variables were binary (0 = absence, 1 = presence of the condition), while continuous variables (age, duration of exposure, time from removal and FEV₁) were transformed into categorical variables with the quartile distribution obtained from all patients; in particular, the highest quartile (for age, duration of exposure and time to removal) or the lowest quartile (for FEV₁) was associated with the presence of the condition.

Results

The clinical features of patients at diagnosis, subdivided by the presence or absence of a follow-up visit, are reported in table 1. There was not significant difference between the two groups of asthmatic patients regarding

Table 1. Clinical and functional characteristics of all patients, subdivided by the presence or absence of a follow-up visit

	With FU	Without FU
Patients	46	35
Mean age $\pm$ SD, years	47.06 $\pm$ 10.9	40.23 $\pm$ 13.3
Males/females	32/14	29/6
Smoker, %		
Yes	17.3	15.2
No	45.7	49.7
Ex-smoker	37.0	35.1
Atopy, %	22.2	18.0
Mean FEV ₁ $\pm$ SD, %pred.	80.7 $\pm$ 18.4	87.2 $\pm$ 11.3
PD20FEV ₁ <1.0 mg, %	80.4	61.1
Type of asthmatic reaction to SIC, %		
Early	42	48
Late	30	26
Dual	28	26

FU = Follow-up.

Table 2. Clinical and functional characteristics of the patients examined at baseline and at follow-up

	Diagnosis	Follow-up	p
Asthma severity, %			
Intermittent	25.4	47.2	
Mild persistent	6.4	16.6	
Moderate persistent	32.1	15.4	<0.05
Severe persistent	37.1	10.8	
Mean FEV ₁ $\pm$ SD, %pred.	80.7 $\pm$ 18.4	86.2 $\pm$ 25.1	<0.05
PD20FEV ₁			
(geometric mean), mg	0.23 (n = 43)	0.42 (n = 37)	<0.01
PD20FEV ₁ >1.0 mg, %	11.6 (n = 5)	35.1 (n = 13)	

their characteristics at diagnosis, although patients who had a follow-up visit were older, with a lower FEV₁ and had a greater prevalence of bronchial hyperresponsiveness at diagnosis.

In table 2, the characteristics of patients with a follow-up examination were reported at the time of diagnosis and at the follow-up visit. Total duration of work exposure at diagnosis was 22.3 $\pm$ 13.3 years. Moderate and severe levels of asthma severity were significantly reduced at follow-up with respect to diagnosis. In the whole group, there was a significant improvement in FEV₁ (% predicted) and PD20FEV₁ methacholine at the follow-up as compared with values observed at diagno-

sis ($p < 0.05$ and $p < 0.01$, respectively). At diagnosis, 11.6% of patients had a PD20FEV₁ >1.0 mg, whereas at follow-up, this percentage was 35.1%. In 12 out of 35 patients who had a methacholine challenge performed both at baseline and at follow-up, the ratio between PD20FEV₁ methacholine measured at the follow-up and at diagnosis was >2 (which is considered a significant improvement in bronchial hyperresponsiveness). At the time of diagnosis, only 42% of patients were under regular treatment with anti-asthma drugs, while at the follow-up visit, 30% of the patients did not use anti-asthma drugs, 28% used inhaled short-acting bronchodilators only, and 42% used inhaled corticosteroids and long-acting bronchodilator combinations.

At follow-up, 32 patients had been removed from exposure (mean removal from exposure 6.0 $\pm$ 6.9 years), whereas 14 patients continued to work, but remained indirectly exposed to TDI because they were moved to a different job in the same factory where TDI exposure was occasional. Subdividing patients at the follow-up by the persistence or withdrawal from occupational exposure, the comparison between the prevalence of asthma-like symptoms at baseline and at follow-up examination in patients still exposed did not show any differences; there was a significant reduction in the presence of attacks of shortness of breath and dyspnoea at the follow-up examination in patients no longer exposed to TDI (fig. 1). Because baseline FEV₁ may be an important determinant of the outcome of asthma, we divided the patients in two groups according to FEV₁ measured at diagnosis (lower or higher than 82% predicted, the median value of the FEV₁ distribution), and in these two groups, we evaluated the changes in FEV₁ and bronchial hyperresponsiveness to methacholine at the follow-up (table 3). Patients who had ceased work showed a significant increase in FEV₁ and a significant improvement in bronchial hyperresponsiveness only in the group with a lower FEV₁ at diagnosis, and not in the group with a higher FEV₁ at diagnosis. On the other hand, subjects who continued to work had no improvement in FEV₁ and bronchial hyperresponsiveness independent from the baseline FEV₁.

Logistic regression analysis, using different models with all or some of the independent variables, showed that there were no significant determinants of improvement in FEV₁ (table 4), while a shorter duration of symptoms before diagnosis was a significant predictor of improvement in PD20FEV₁ methacholine at follow-up (table 5). Cessation of exposure showed only a trend in the improvement in FEV₁ in some models.

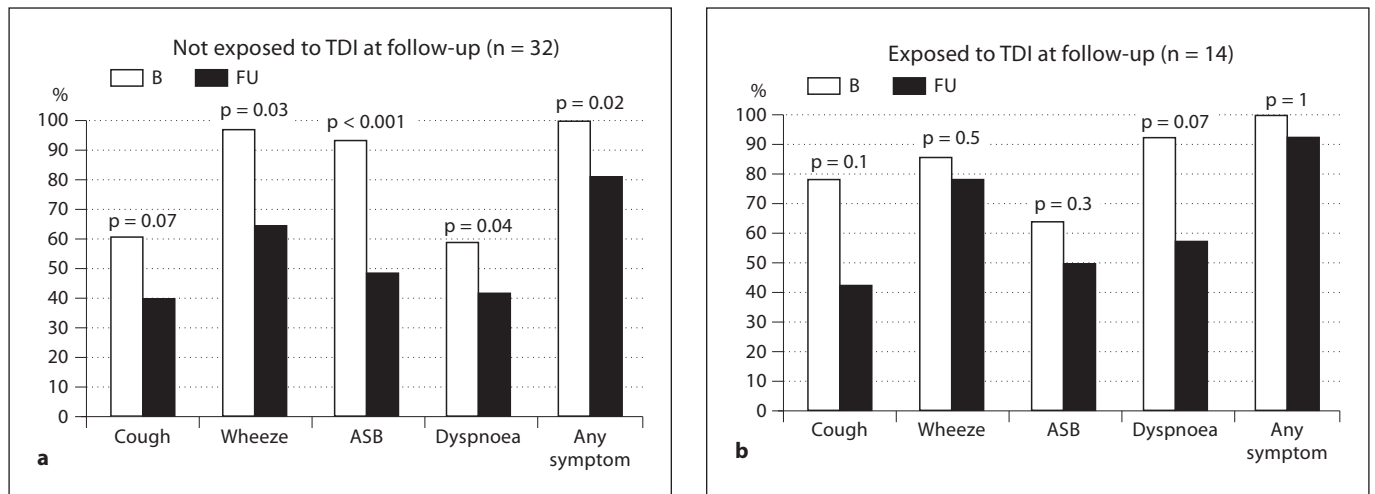


Fig. 1. Prevalence of asthma-like symptoms at baseline (B, white columns) and at follow-up (FU, black columns) in the examined patients, according to cessation (a) or persistence (b) of occupational exposure to TDI at the time of follow-up. ASB = Attacks of shortness of breath.

Table 3. Mean values of FEV₁ and PD20FEV₁ methacholine at baseline and follow-up, according to the level of FEV₁ at diagnosis (lower or higher than 82% predicted) and the persistence or cessation of occupational exposure to TDI

	Exposed (n = 14)				Not exposed (n = 32)			
	FEV ₁ <82% (n = 5)		FEV ₁ ≥82% (n = 9)		FEV ₁ <82% (n = 17)		FEV ₁ ≥82% (n = 15)	
	baseline	follow-up	baseline	follow-up	baseline	follow-up	baseline	follow-up
ICS therapy, %		100		34		65		21
Mean FEV ₁ ± SD, %pred.	73.7 ± 6.3	74.5 ± 15.6	99.6 ± 11.9	97.0 ± 18.1	64.8 ± 6.8	76.6 ± 13.0*	92.4 ± 6.1	89.1 ± 8.9
PD20FEV ₁ (geometric mean), mg	0.09	0.06	0.49	0.58	0.20	1.01*	0.21	0.25

ICS = Inhaled corticosteroid. * p < 0.05 from baseline.

Discussion

This study describes the clinical features of 46 patients with TDI-induced asthma and the outcome of these patients after a long-term follow-up. We confirmed that there was a general improvement at follow-up in all markers of asthma severity (symptoms, asthma severity, pulmonary function and bronchial hyperresponsiveness), particularly in patients who have ceased occupational exposure to TDI and in those with a lower baseline FEV₁, and that the duration of symptoms before diagnosis was the main determinant of improvement in methacholine responsiveness at follow-up.

The results of this study confirm some features of TDI asthma: low proportion of atopic subjects and current smokers, long duration of exposure and symptoms before diagnosis. At follow-up, 32 out of 46 patients had been removed from exposure, while only 14 patients continued to remain exposed to TDI, although to a lower level of TDI due to a change in the specific job. Nevertheless >80% of patients still reported asthmatic symptoms and many of them were still hyperreactive to methacholine. In particular, patients who were still exposed to TDI (although to a lower level with respect to the baseline examination) continued to report asthma-like symptoms at follow-up examination, and FEV₁ and PD20FEV₁ have

Table 4. Logistic regression analysis for the assessment of baseline determinants of improvement in FEV₁ at follow-up, using model 1

	OR	95% CI	p
Model 1			
Removal from exposure	3.6	0.8–15.9	0.09
Exposure duration	1.3	0.2–7.5	n.s.
Baseline FEV ₁	1.0	0.2–4.7	n.s.
Baseline PD20FEV ₁	0.8	0.2–4.3	n.s.
ICS therapy	0.5	0.09–2.5	n.s.
Symptom duration	0.3	0.05–1.9	n.s.

Dependent variable: Δ FEV₁ %pred. >1%. OR = Odds ratio; CI = confidence interval; n.s. = not significant.

Table 5. Logistic regression analysis for the assessment of baseline determinants of improvement in PD20FEV₁ methacholine at follow-up, using different models

	OR	95% CI	p
Model 1			
Symptom duration	0.1	0.02–1.1	0.06
Exposure duration	2.8	0.3–23.2	n.s.
ICS therapy	1.3	0.3–6.8	n.s.
Baseline FEV ₁	0.5	0.09–2.9	n.s.
Removal from exposure	0.7	0.4–4.1	n.s.
Baseline PD20FEV ₁	0.8	0.1–4.8	n.s.
Model 2			
Symptom duration	0.1	0.02–0.9	0.04
Exposure duration	2.9	0.4–22.5	n.s.
Baseline FEV ₁	0.5	0.08–2.5	n.s.
Removal from exposure	0.7	0.1–3.8	n.s.

Dependent variable: PD20FEV₁ ratio >1.5. OR = Odds ratio; CI = confidence interval; n.s. = not significant.

not improved. On the other hand, patients who have ceased work had a significant improvement in symptoms, in the level of asthma severity as well as in bronchial hyperresponsiveness. Interestingly, this improvement was observed only in patients with a lower FEV₁ at diagnosis and who have ceased work, suggesting that baseline pulmonary function was a major determinant, better than work exposure, of the outcome of TDI-induced asthma after diagnosis.

In agreement with some [7] but not with other reports [3, 4], duration of symptoms before diagnosis (and then before removal or reduction in TDI exposure) was the main determinant of improvement in bronchial hyper-

responsiveness, confirming that the duration of the disease is crucial in order to obtain some regression of the inflammatory and structural changes of the airways, as in non-occupational asthma [12].

These findings are in partial agreement with the results of previous studies. In 2003, Padoan and coworkers [4] performed a long-term follow-up study on patients with TDI-induced asthma. They examined 87 subjects and they found that the respiratory symptoms and airway hyperresponsiveness to methacholine improved in patients removed from exposure to TDI for a long period. A more favourable prognosis was associated with a better lung function and a lower degree of airway hyperresponsiveness to methacholine at diagnosis. In 2000, Piirila et al. [3] examined 233 subjects with isocyanate-induced asthma to study the clinical outcome in a long-term follow-up study. Persistence of symptoms and non-specific bronchial hyperresponsiveness were associated with the exposure to TDI or diphenylmethane diisocyanate rather than to examethylen diisocyanate.

In a recent paper, Rachiotis et al. [6] report a systematic review of the published literature on the symptoms and functional outcomes of occupational asthma carried out after avoidance of exposure to the causative agent. Reported rates of symptomatic recovery varied from 0 to 100%; these rates were lower with increasing age, and patients with the shortest durations of exposure had the highest rate of recovery, without linear effect. The pooled prevalence of persistent bronchial hyperresponsiveness at follow-up was 73%, and this was higher among patients whose disease was due to high-molecular-weight agents. In between study comparisons, no clear patterns of improvement relating to the total duration of exposure or follow-up were found. From within-study comparisons there was some evidence that a shorter duration of symptoms was associated with a higher rate of symptomatic recovery. Considerable heterogeneity in these findings has been identified, and the available data on the prognosis of occupational asthma seem to be insufficiently consistent to allow confident advice to be given to the patients with the disease.

In comparison with previous reports on the same topic, our study has some specific characteristics not considered in the majority of the previous papers: (1) only patients with TDI occupational asthma were studied, while several papers included a combination of patients with occupational asthma induced by different agents; this is particularly relevant considering the different outcome of asthma according to the type of aetiological agent (high- vs. low-molecular-weight compound) [6]; (2) in all pa-

tients, the diagnosis was made by specific inhalation challenge, making the diagnosis of occupational asthma more accurate; (3) the follow-up time was long (>10 years), offering an additional contribution to the previous studies. Only the studies by Padoan et al. [4] and Piriila et al. [3] had a long-term follow-up of diisocyanate-induced asthma and a isocyanate inhalation test at the time of diagnosis. However, the study by Padoan et al. [4] showed that only baseline PD20FEV₁ methacholine was a predictor of improvement in bronchial hyperresponsiveness at follow-up, while the study by Piriila et al. [3] used as its primary objective the comparison among asthma induced by different diisocyanates, and only marginally reported data on the long-term outcome of this disease.

In agreement with earlier reports [4, 8], the use of anti-inflammatory drugs for asthma did not modify the outcome of clinical and functional data. In a short-term follow-up after cessation of exposure, it was demonstrated that airway inflammation persisted in diisocyanate-induced asthma, despite inhaled corticosteroid medication [13].

Our study has some limitations. First of all, the number of patients studied is fairly small, although collected in a single centre. Secondly, the patients with a follow-up examination seem to have slightly, although non-significant, greater asthma severity at diagnosis, and therefore, it is possible that more severe patients have been more compliant to the follow-up examination, with a lower probability of improving. Thirdly, patients who have ceased work tended to have a greater severity of the disease at diagnosis, and this may have contributed to the decision of ceasing work. However, the baseline characteristics of our patients are similar to those reported in other papers [6] which have the same limitations in the selection of patients.

In conclusion, our study supports previous studies showing that asthma-like symptoms, bronchial hyperresponsiveness and airway obstruction slightly improve but do not normalize after a long period after cessation or reduction in TDI exposure. Our results emphasize, in agreement with current recommendations [1, 14], the need for adequate medical surveillance which may allow an early diagnosis and, when possible, a consequently early removal from or a reduction in occupational exposure.

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