

Toluene diisocyanate induced asthma: outcome according to persistence or cessation of exposure

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Abstract

Sixty patients with occupational asthma due to exposure to toluene diisocyanate (TDI) were re-evaluated, five years after the initial diagnosis had been confirmed by a specific bronchial provocation challenge. During both examinations the severity of asthmatic symptoms and the need for antiasthma treatment were graded and lung function tests, measurement of airway responsiveness to methacholine (PD₁₅), and skin tests with common inhalant allergens were carried out. The evolution of the disease was established on the basis of the increase or decrease in asthmatic symptoms, requirements for medication, and FEV₁ and PD₁₅ methacholine between the two examinations. At follow up 17 patients (group A, 28.3%) had carried on working in the same environment after relocation to jobs with only occasional exposure to TDI; 15 of them used protective respiratory devices. The remaining 43 (group B, 71.7%) avoided further inhalation of TDI by moving to another sector. Group A showed a significant decrease in FEV₁ and PD₁₅ methacholine and significant increases in the severity of symptom score and requirement for medication; 13 subjects (76.5%) were worse, four (23.5%) were stable, and no one had recovered or improved. Group B showed significantly less severe symptoms and a threefold increase in PD₁₅ methacholine; 12 subjects (28.2%) totally recovered, 10 (23.2%) improved, 16 (37.2%) were stable, and five (11.6%) were worse. In group B the duration of exposure to TDI and of symptoms before the initial diagnosis delineated the patients who recovered from those who did not improve; intermediate values in these features characterised the subjects who improved but did not recover. It is inferred that complete removal

from exposure is the only effective way of preventing deterioration in patients with occupational asthma due to TDI. Early diagnosis and early removal from exposure after the onset of asthma are important factors for a favourable outcome of the disease.

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Isocyanates, particularly toluene diisocyanate (TDI), are the agents responsible for a large proportion of occupational asthma in Italy and have been responsible for about 47% of the cases of asthma due to occupational sensitisers in the past 10 years.¹

Several questions remain unanswered regarding the natural course of the disease. One question, vital for its practical implications, is whether in sensitised subjects the reduction of exposure and the use of appropriate medication can be as effective as that of leaving the job in preventing clinical deterioration. Little information is available on this topic as not much is known about TDI induced asthma in patients who decided to carry on working in the same industry.²⁻⁵ Uncertainty also exists as to the outcome of TDI induced asthma after stopping exposure and as to what factors affect the prognosis. We found eight follow up studies on workers with TDI induced asthma who avoided further exposure to the substance after confirmation of the diagnosis.²⁻⁹ Recovery was found in a variable proportion of subjects that ranged from 19%⁶ to 86%²; also the factors affecting the outcome varied considerably. Some authors considered that the persistence of asthma was due to duration of exposure to TDI.^{4,7} Others attached great importance to the patients' pulmonary condition at diagnosis or to the type of asthmatic reaction to the TDI inhalation challenge.^{5,8,9} One study was unable to find any feature, at the time of the diagnosis, that subsequently distinguished the patients who recovered from those who did not. It is likely that part of the difficulty in solving these questions is due to the few subjects evaluated and to the different duration of the follow up, which often ranges from months to years in patients of the same report.

To retrieve more data on the natural history of the disease we performed a follow up study on a con-

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siderable number of workers with asthma due to TDI sensitisation, all of whom were re-evaluated five years after the initial diagnosis had been confirmed by a specific inhalation challenge test; they were representative of the total cases with TDI induced asthma assessed between 1980 and 1985 in our hospital.

Methods

All 65 patients with TDI induced asthma diagnosed between 1980 and 1985 in our hospital were recalled five years (± 7 months) later; they were informed that re-examination was not to assess disability for compensation but to update the knowledge of their health.

Sixty workers accepted, (five were not traced); 53 of them were spray painters who used polyurethane paints, three produced polyurethane varnishes, three manufactured polyurethane foams, and one soldered electric wires coated with polyurethane resins.

At diagnosis all subjects filled in a questionnaire: information was obtained about the characteristics of the risk of exposure to TDI at the workplace (continuous or intermittent exposure, use of protective respiratory devices, presence of ventilation), the severity of the asthmatic symptoms, need for medication, and stays in hospital for asthma over the past 12 months. Symptoms were graded as grade 0 (no wheezing or chest tightness); grade 1 (occasional episodes of wheezing or chest tightness); grade 2 (weekly episodes of wheezing or chest tightness); grade 3 (daily occurrence of the symptoms); grade 4 (grade 3 plus a stay in hospital). The need for antiasthmatic medication was assessed using the scale: grade 0 (no medication); grade 1 (use of β_2 agonist when necessary); grade 2 (daily use of β_2 agonist); grade 3 (daily use of β_2 agonist and inhaled steroids or systemic methylxanthine preparations); grade 4 (grade 3 plus the use of systemic corticosteroids).

All subjects underwent (1) skin tests with a battery of 15 common inhalant allergens, using the intradermal method; a reaction was considered positive when a weal diameter was at least half of that brought about by a histamine control solution; atopy was regarded as present when one or more positive reactions were elicited. (2) Lung function tests: inspiratory vital capacity (VC) and forced expiratory volume in one second (FEV_1) were measured according to the recommendations of the European Community for Coal and Steel (ECCS)¹⁰ with a pneumotachograph instrument (Transferscreen Jaeger, Wurzburg). Subjects were studied in the standing position with nose clips. All subjects had been free of respiratory infections for at least two weeks and had not been exposed to TDI for at least one week. None had taken cromolyn, theophylline, sympathomimetic

drugs, or corticosteroids 48 hours before examination. Reference values were those of the ECCS.¹¹ Lung function was considered impaired when VC or FEV_1 was $< 80\%$ of that predicted; an obstructive type of ventilatory defect was diagnosed when FEV_1 was less than 80% of that predicted and was associated with a reduction in FEV_1/VC . (3) A methacholine inhalation test was performed with a Mefar dosimeter according to the protocols of the Italian Societies of Respiratory Pathophysiology and of Occupational Medicine for non-specific bronchial provocation tests.¹² Dose response curves to methacholine were obtained by plotting the baseline value for FEV_1 and the value after each methacholine dose against the cumulative dose of methacholine delivered, on a log scale; the cumulative dose of methacholine producing a 15% fall in FEV_1 (PD_{15}) was calculated by interpolation from the dose-response curve. A subject was regarded as hyper-reactive to methacholine when his PD_{15} was 1 mg or less. (4) Inhalation challenge to TDI: the subjects were exposed to 0.02 (SD 0.004) ppm of 2,4-2,6 TDI vapours (80 : 20) generated in a 7 m³ exposure chamber by heating 0.035 ml of isocyanate on a watch glass at 60 °C, with a fan in the room. The duration of exposure was up to 20 minutes unless there was an earlier appearance of respiratory symptoms. On the day of the challenge FEV_1 was monitored every 15 minutes for one hour before exposure. The largest of the first three technically satisfactory FEV_1 values was recorded; this was not to be less than 95% of FEV_1 recorded on the day of the baseline lung function study and maximum variations were not to be greater than 5% to carry on with the test. The FEV_1 value assessed immediately before the exposure to TDI was chosen as the baseline FEV_1 of the day of the TDI challenge. After the exposure FEV_1 was measured at 15, 30, and 60 minutes, then hourly for eight hours, and finally after 24 hours. A challenge test was deemed positive when there was at least a 15% fall in FEV_1 associated with a pattern suggesting sustained bronchial obstruction (sustained fall in FEV_1 and wheezing at clinical examination). The asthmatic reactions were classified as early if they developed within 30 minutes after exposure to TDI, late if they developed an hour or more after the exposure, or dual if an immediate reaction was followed by a spontaneous return of FEV_1 to the baseline value whereupon a second FEV_1 decrease occurred.¹³

At the follow up examination all patients were questioned about their working conditions since diagnosis (a different job in another industry, the same or different job in the same industry, possible presence of irritant substances for the airways, possible change in the use of protective respiratory devices, or improvement of ventilation at the same workplace). They were also asked about the severity

of the asthmatic symptoms, the need for asthma medication during the past year, and the occurrence of stays in hospital since the diagnosis. Gradation of symptoms and of medication was done in the same way as at diagnosis. A change in symptom score or medication score by one grade was regarded as significant.

Skin tests for allergy, lung function tests, and bronchial challenge with methacholine were repeated.

A decrement or increment in FEV₁ of more than 10% was regarded as a significant change.

When PD₁₅ methacholine in a patient was at least twofold or half of that recorded at the first examination, this was regarded as a significant change in his bronchial reactivity. Annual loss of FEV₁ was also calculated for each subject as:

$$\frac{\text{Initial FEV}_1 \text{ value} - \text{final FEV}_1 \text{ value}}{\text{Months of follow up}} \times 12$$

A subject was regarded as recovered when he had been symptom and medication free for at least the past 12 months and his lung function tests and airways responsiveness to methacholine were within the normal range; he was regarded as improved or deteriorated if he showed a significant improvement or deterioration in his symptom score or requirement for medication together with a significant improvement or deterioration in the FEV₁ baseline value or PD₁₅ methacholine; those who did not fulfil these criteria were considered stable.

STATISTICAL ANALYSIS

Comparison of ratios was carried out with the χ^2 test; comparison of means was by Student's paired and unpaired *t* tests. The level of statistical significance was set at $p \leq 0.01$.

Results

At the time of the follow up examination, 17 patients (group A, 28.3%) were still working in the same

environment and 43 (group B, 71.7%) were no longer exposed to TDI because they had moved to another industry.

The comparison of the patients' conditions at diagnosis (table 1) showed that the subjects of group A were older and had had longer exposure to TDI.

Difficulty in finding a new job and the possibility of relocation to an area with discontinuous exposure were the reasons that induced them not to leave their present occupation. At re-evaluation, all 17 patients were assigned to tasks with an only occasional risk of TDI inhalation; all but two regularly used protective respiratory devices (paper masks or twin cartridge respirators); none reported a change in ventilation at the workplace.

Subjects of group B had moved away from exposure within six months after the diagnosis so they had had no inhalation of TDI for about four and a half years when re-examined.

Table 2 reports the clinical data at diagnosis and at follow up in the 60 patients. No patient had changed his smoking habits between the two examinations and the number of atopic patients was the same. The group of subjects with persistent occupational exposure to TDI showed a significant decrease in VC, FEV₁, FEV₁/VC, and PD₁₅ methacholine and a significant increase in the severity of asthmatic symptoms and the need for appropriate treatment (paired *t* test after five years). Four subjects (23.5%) were considered stable, 13 (76.5%) had deteriorated, and none had improved or recovered.

At re-evaluation, the group of workers who had avoided further exposure had significantly less severe symptoms and a threefold increase in PD₁₅ methacholine than at diagnosis (paired *t* test). Twelve subjects (28%) had completely recovered, 10 (23.2%) had improved but still required treatment for asthmatic symptoms, 16 (37.2%) were stable, and five (11.6%) were worse.

Although the symptoms score, medication score, lung function tests, and PD₁₅ methacholine of group

Table 1 Characteristics of 60 subjects with TDI induced asthma at the time of diagnosis according to persistence or cessation of exposure at follow up examination

Characteristics	Group A (n = 17) Still exposed	Group B (n = 43) No longer exposed
Age (y)	43.6 (SD 9)*	34.8 (SD 12.5)
Smoking habit:		
Smokers	3 (17.6%)	6 (13.9%)
Non-smokers	14 (82.4%)	37 (86.1%)
Atopic state	2 (11.7%)	6 (13.9%)
Subjects with symptoms of asthma before exposure to TDI	1 (5.9%)	2 (4.6%)
Duration of exposure to TDI (y)	25 (SD 7.9)***	11.5 (SD 9.5)
Duration of symptoms before diagnosis (y)	6.3 (SD 4.7)	3.7 (SD 3.5)
Type of asthmatic reaction induced by TDI challenge:		
Immediate	9 (53%)	12 (28%)
Dual	4 (23.5%)	11 (25.5%)
Late	4 (23.5%)	20 [46.5%]

* $p < 0.01$; *** $p < 0.001$ (unpaired *t* test between groups).

Table 2 Clinical details of 60 patients at diagnosis and at follow up

Characteristics	Group A (n = 17)	Group B (n = 43)
	Still exposed Mean (SD)	No longer exposed Mean (SD)
Symptom score:		
At diagnosis	1.7 (0.8)	1.8 (0.8)
At follow up	2.3† (1.1)***	0.9††† (0.8)
Medication score:		
At diagnosis	1.4 (1)	1.1 (0.7)
At follow up	2.8††† (1)***	0.9 (1.2)
VC (% predicted):		
At diagnosis	98.1 (14.2)	98.3 (12)
At follow up	89.2†† (10.6)	96.7 (15.6)
FEV ₁ (% predicted)		
At diagnosis	86.8 (22.5)	92.7 (16.5)
At follow up	72.9††† (19.4)**	91.9 (20.8)
FEV ₁ /VC:		
At diagnosis	66.4 (11.7)	73.5 (10.7)
At follow up	60.1† (13.5)**	72.9 (13.5)
PD ₁₅ , methacholine (μg):		
At diagnosis	425 (608)	498 (357)
At follow up	301††† (610)***	1617††† (1567)

*p < 0.01; **p < 0.005; ***p < 0.001 (unpaired *t* test between groups).

†p < 0.01; ††p < 0.005; †††p < 0.001 (paired *t* test between initial and follow up examination).

A and B were similar at the time of the diagnosis they became significantly different at follow up (unpaired *t* tests). The rate of decline of FEV₁ was 120 (SD 128 ml/y) in patients of group A and 12 (SD 88) ml/y in group B; again the difference was significant on unpaired *t* test analysis. To find out what factors affected the prognosis of the TDI induced asthma in subjects who had left their workplace, group B was divided into three subsets according to the clinical outcome (group I, recovered; group II, improved; group III, not improved—that is, stable plus deteriorated) and their initial data were compared (table 3). Irritant factors for the airways (dusts, fumes or gases) were present in the new workplace in one of the 12 (8.3%) subjects who had recovered, in

four of the 10 (40%) patients who had improved, and in five of the 21 (23.8%) who had not improved; the ratios were not statistically different on χ^2 analysis. The duration of exposure to TDI and of symptomatic work was significantly shorter in patients who had recovered than in those who had not improved at all; intermediate values characterised the subjects who had improved but had not completely recovered. None of the workers who recovered had had occupational exposure to TDI longer than 10 years and a duration of exposure after the onset of asthmatic symptoms longer than three years.

It was not possible to analyse group A the same way as group B as there were no recovered patients and too few who had improved.

Discussion

In this study we examined the characteristic features of 60 patients with occupational asthma due to TDI five years after the initial diagnosis according to the persistence or not of exposure to the offending agent.

We found that in most of the group who had decided to continue working in the same environment, relocation to a job with discontinuous exposure, the use of protective devices, or treatment were unable to prevent the worsening of asthmatic symptoms and further damage to the airways. In particular, the yearly loss in FEV₁ was about fourfold in these patients compared with normal subjects¹⁰ and double that seen in patients with non-occupational asthma.¹⁴ Similar results were described by Innocenti *et al.*,² Paggiaro *et al.*,³ Rosenberg *et al.*,⁴ and Mapp *et al.*⁵ in the specific case of workers with TDI induced asthma and by Chan-Young *et al.*¹⁵ and Cote *et al.*¹⁶ in cases of workers continuously exposed to western red cedar.

Table 3 Characteristics of 43 subjects who moved away from exposure to TDI after diagnosis, according to their outcome at the time of follow up examination

	Recovered subjects (Group I, n = 12)	Improved subjects (Group II, n = 10)	Non-improved subjects (Group III, n = 21)
Age (y)	29 (11.4)	33 (12.1)	38.9 (12.4)
Smoking habit:			
Smokers	2 (16.7%)	1 (10%)	5 (23.8%)
Non-smokers	10 (85.3%)	9 (90%)	16 (76.2%)
Atopic state	0	2 (20%)	4 (19%)
Subjects with symptoms of asthma before exposure to TDI	0	0	2 (9.5%)
Duration of exposure to TDI (y)	6.3 (4.1)*	10 (7.4)	15.9 (11.1)
Duration of symptoms before diagnosis (y)	1.6 (1.2)**	2.8 (1.9)	5.4 (3.9)
Symptom score	1.9 (0.8)	1.9 (0.7)	1.9 (0.9)
Medication score	1 (0.8)	1.2 (0.6)	1.2 (0.6)
FEV ₁ (% predicted)	92.5 (14.7)	90.1 (14.8)	94 (17.7)
PD ₁₅ , methacholine (μg)	646 (390)	478 (364)	424 (304)
Type of asthmatic reaction induced by TDI challenge:			
Immediate	4 (33.3%)	2 (20%)	6 (28.5%)
Dual	2 (16.7%)	3 (30%)	6 (28.5%)
Late	6 (50%)	5 (50%)	9 (43%)
% Maximum fall in FEV ₁ in TDI challenge	37.4 (17.8)	34.5 (14.3)	37.9 (16.2)

*p < 0.01; **p < 0.005 (unpaired *t* test between groups I and III). Nos in parentheses are SD unless otherwise stated.

These findings suggest that complete removal from exposure is the only appropriate way of preventing deterioration in patients with occupational asthma.

This approach does not, however, necessarily lead to recovery. In fact, four years after completely stopping inhalation of TDI, not more than a quarter of the 43 patients were symptom and medication free and had normal lung function tests and airway responsiveness to inhaled methacholine. Roughly another quarter had milder symptoms and had less severe non-specific bronchial hyperreactivity than at diagnosis. We cannot rule out the possibility that asthma will disappear in them with time although it had been shown that a plateau of improvement in workers with occupational asthma is reached about one year after stopping exposure for spirometry, and two years after stopping exposure for bronchial hyperresponsiveness.¹⁷ Nevertheless, the significant proportion of subjects who had unchanged symptoms of bronchoconstriction and non-specific bronchial hyperreactivity show that asthma due to TDI could give rise to permanent respiratory consequences.

The percentage of our patients still asthmatic at follow up (with the same or milder severity) was comparable with the 41 out of 50 (82%), eight out of 12 (66%), and 27 out of 30 (77%) respectively reported by Lozewicz *et al*,⁸ Paggiaro *et al*,³ and Mapp *et al*,⁵ but higher than the 13 out of 50 (26%) and 10 out of 20 (50%) reported by Innocenti *et al*² and Rosenberg *et al*.⁴

As to what factors can affect the prognosis we found that persistence of asthma was associated with the duration of exposure to TDI and of symptoms at work before diagnosis. No other clinical feature at the initial examination delineated improved patients from non-improved patients at follow up. Clinical tests included the degree of non-specific bronchial reactivity and the type and severity of asthmatic reactions induced by the inhalation challenge test to TDI. Also the quality of the new worksite (that is, the amount of non-specific pollutants) did not seem to play a part in the outcome of the disease. These data, in agreement with some of the previous follow up studies on TDI induced asthma after stopping exposure,^{4,7} emphasise the importance of an early

diagnosis and early removal from exposure after the onset of asthma for a favourable outcome of the disease, rather than host factors.

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